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Volume 4
Issue 1-4
2019

Official Journal

ISSN 2240-5127 (print)
www.progressneuroscience.com
Authorized by the Tribunale in Trento, 11 maggio 2011 - Registration: Registro della Stampa n. 18 and Registro degli Operatori di Comunicazione (ROC) n. 3810 - *Quarterly* -
€ 20,00

Progress in
Neuroscience

An interdisciplinary journal

SNO CIENZE EUROLOGICHE SPEDALIERE
Official Journal

ISSN 2240-5127
Volume 4, Issue 1-4, March-December 2019

INDEX

COVER: La Desintegración de la Persistencia de la Memoria (The Disintegration of the Persistence of Memory), oil on canvas, painting by the Spanish surrealist Salvador Dalí in 1952.

NEUROTOPICS

Dementia: where we stand?

Edited by

CRISTINA PACI

Details from some William Utermohlen's self-portraits. This American artist received a diagnosis of probable Alzheimer's disease in 1995, at the age of 61. For the next five years, as his dementia worsened, he used his art to track the disintegration of his mind (Dates of these paintings: 1967, 1996, 1997, 1998, 1999, 2000).

Progress in Neuroscience 2019; 4 (1-4).
ISSN: 2240-5127

Editorial

Dementia

Dear collegues, we wish to introduce a new volume of the Italian Society of hospital Neuroscience (SNO) in which we describe reviewes of the most frequent neurodegenerative dementias.

Neurodegenerative dementias need not only a neurological investigation but also neuroradiological and neurosurgical study. SNO comprises such specialities and its multidisciplinary characteristic enables it to reach its goal

The volume contains a review of Alzheimer disease, fronto-temporal disease, Lewy body disease, differential diagnosis of dementia by neuroimaging and hydrochephalus dementia.

All papers describe the new guideline for the classification of the different neurodegenerative pathologies.

We know that there are many published articles on the subject , so SNO decided to publish an updated volume of neurodegenerative dementias as a reference for specialists.

We hope you will appreciate the volume and invite you all to publish scientific works in our official SNO journal to increase communication among neuroscience hospital specialists, thus improving our work.

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Progress in Neurosciences 2019; 4 (1-4): 5.
ISSN: 2240-5127
doi: 10.14588/PiN.2019.Paci.5

Review

□ Alzheimer's dementia

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SUMMARY: *I was given the task of reviewing current knowledge on Alzheimer's disease. Each of us, professional clinician, is daily confronted with cases and persons of disparate origin who complain of memory failures and increasing disorientation or naming difficulties with aging. The diagnosis is often very simple. However not necessarily our guess meets the canonical criteria designed by our colleagues who are mainly involved in research. Literature on the topic is vast and anyone can absorb desired information to guide clinical skills and treatment methodologies over the myriads of scientific papers or international meetings. There is no need to provide you with a boring summary of what is known in the field since last twenty-five years. It would be more profitable, I hope, to share with you our personal clinical experience hoping to open new windows and unexplored trails which can more adequately address the real needs of our patients starting with a better recollection of the history of their life, long time before they eventually develop the disease.*

KEY WORDS: *Amyloid beta Alzheimer Dementia, CT, Cerebrospinal fluid, FDG, Magnetic Resonance, PET.*

Aging is not a disease. Good aging however is a luxury not for many.

Today, our society cannot allow to bear heavy loads. Bad (pathological) aging becomes a double disease. First for those affected (*at an individual level*); secondly for the entire society, upon which all incident cases impact (*social or group level*). Nobody is yet prepared to adequately overcome this new epidemic, nor our society, or our public health system. Even less prepared are caregivers, often left alone to fight the very challenging and devastating battle of populations' aging.

Dementia is a biological process of cerebral degeneration, which reduces and thins neurons and knowledge within the human brain, progressively and irreversibly. It begins in a subtle way but soon becomes inexorable. The affected individual is not completely aware of her/his difficulties; relatives also minimize at first the magnitude of their symptoms and the impact on everyday life. Very often these failures become apparent around the retirement phase of life and easily these are misdiagnosed as "depressive" reactions. Instead this is a very slow neurodegenerative process of exfoliation of premorbid acquired skills, which has no equals in neuropathology, where cerebral, and cognitive rearrangements finally result devastating. Among all forms of dementia, Alzheimer's disease represents almost 50% of all recognized cases[16].

Current research assumes that 1% of western population might be affected by Alzheimer's disease at age 60. This rate doubles every 5 years, so at age 80 almost 16% of resident population results affected by the disease, and at age 90, more than half of

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Progress in Neuroscience 2019; 4 (1-4): 7-13. *ISSN: 2240-5127*
doi: 10.14588/PiN.2019.Zappalà.7

LIST OF ACRONYMS AND ABBREVIATIONS: **Abeta** = Amyloid beta; **AD** = Alzheiemer's Disease; **CSF** = CerebroSpinal Fluid; **FDG** = Fluoro-Dexosi-Glucose; **MRI** = Magnetic Resonance Imaging; **PET** = Positron Emission Tomography.

survived individuals might be affected by such pathological process. Early forms of dementia of Alzheimer's type (age 40 to age 60) although less frequent, are diagnosed as well; their pathological and clinical progression is actually worse and faster. In Italy it is calculated that 12 new cases/1000/year could be an overall good estimate for those individuals over 65 years of age. Therefore almost 100.000 new cases are diagnosed every year with early or advanced clinical symptoms of this degenerative form of dementia.

Alzheimer's disease was labeled after Alois Alzheimer and Gaetano Perusini's description of a relatively young lady manifesting with cognitive as well as behavioral disturbances which were not related to any known disease at that time. It was discovered more than a hundred years ago, however only in the last twenty years there has been sufficient recognition and improved medical care for patients affected and their caregivers. Since 1984, when diagnostic criteria were first generated[13] our perception of the disease and our clinical approach has completely changed. Also, new criteria are continuously elaborated rearranging our understanding, our approach and our clinical taste. This review will briefly cover a few general topics of the diagnostic process and will soon move to the latest significant selection of newly generated research frameworks.

First, contrary to the old 1984 diagnostic guidelines, Alzheimer's disease covers a continuum from initial changes of asymptomatic subjects to late accumulation of changes characteristics of very old and very severe demented patients. Alzheimer's disease is now labeled "Alzheimer's dementia" to describe patients in the spectrum of the disease, confirmed with neuroimaging and/or cerebrospinal fluid.

Second, initial symptoms are mainly involving short-term or recent memory and the learning system, although very soon language, reasoning, orientation, self-perception, awareness and executive behavior become affected.

Third, as the disease progresses, cognitive, behavioral and functional abilities worsen to the point that people become totally dependent upon others, also for very basic activities of day living, such bathing, eating, or dressing.

The pathological markers of the disease is the accumulation of amyloid beta (between brain neurons) and tau protein (inside the neurons). Beta amyloid plaques deposition contribute to functionally disconnect neurons and synapses. Tau tangles inside the cells block the transport of nutrients and kill the brain neurons[11]. Inflammation due to several causes provokes shrinkage and cell loss contributing to the widespread atrophy. As neuronal damage progresses, the brain can no longer compensate for such changes and the individuals begin to show subtle-to-marked signs of cognitive breakdown. These brain changes start years before clinical manifestation; sometimes twenty or more years. This makes even more difficult our effort of early diagnosis and treatment.

Alzheimer's dementia recognizes various known promoting factors. The first and most acknowledged factor is *age*. Increasing age by itself is the most important factor contributing to trigger the pathological process linked to dementia. Also, *low education* has been found a significant factor by many researchers. Adequate formal education lowers the risk of developing the disease, contributing to build our "cognitive reserve"[17], a sort of "parachute" which delays, slows down the initial manifestation of the disease although never can impede the progression once started. Several *vascular factors* may as well contribute to increase the risk of developing dementia: hypertension, cholesterol, diabetes all contribute to lower the resistance of brain cells under the weight of time and promoting negative factors.

Their contribution has always been postulated in the pathophysiology of dementia, however never fully confirmed. The key point might be the role of these vascular factors upon neurodegeneration itself, due to pro-inflammatory activity now being studied at length. *Familiarity* of dementia is a strong factor, in combination with previous factors, triggered by a genetic predisposition linked to the apolipoprotein E gene[15], especially when two homologous E4 forms are found.

Other important factors, less known and less caught, are *chronic depression*, untreated depression and history of *head trauma*, all factors which inhibit cellular activity at the hippocampal level. The convergence of some of these factors negatively

influences the resistance of the brain apparatus (resilience) and cognitive symptoms start to emerge. If they remain underreported and under investigated, such deviant processes may continue to impact upon the level of cognitive activity which in turn reduces concentration, short-term memory, confidence, and general activity, building up a pathological loop of extreme severity, if left undiagnosed.

A special note deserves a topic often neglected in research and in clinical routine. It is our personal experiences that *general anesthesia*, especially if repeated, long lasting (at least two hours) and after age 55, cumulate a rapid, often devastating pro-inflammatory process that facilitates neuro-degeneration. It is not known at this moment yet, if the anesthetic itself is responsible of the devastation or the prolonged activity under narcosis, but this is a very frequent finding in routine clinical practice (if investigated). Our patients and their relatives come to our laboratories after reporting a recent major surgery, and they often overtly offer such evidence, although clinicians are not ready yet to take into consideration the relevance of such a common event. Very recently, no more than a month ago, a major journal reported cognitive decline in middle-aged individuals who underwent surgery and general anesthesia[2,7]. Reduced concentration, reduced flexibility, reduction in immediate memory and working memory were significantly found and they were correlated to the number of operations and the length of anesthesia. This is a very crucial factor in our experience, increasing the risk of developing dementia in those patients who already have other risk factors (known), serving as a "strong and rapid" stimulator or trigger.

Our patients, and their families complain of such events and we need to listen more carefully. The effect of general anesthesia is visible among individuals who were free of cognitive disturbances; it can be devastating for those who already have developed an initial process of cognitive worsening and cerebral atrophy, as serial neuroradiological and imaging findings show distinctively. In summary, we may list "*general risk factors*" such as chronic consumption of alcohol, vascular pro-inflammatory comorbidities, diabetes, thyroid dysfunction and, "*specific risk factors*" which could be either "genetic" or "epigenetic". Among these, relevant events which occurred during pediatric or adolescence life (*completely neglected*) but also and more importantly during the early mature phase of life, such as traumatic brain injury, untreated depression, neuro-immunitary and dis-immune conditions such as thyroiditis or major allergic reactions.

These mentioned conditions and risk-generating factors all increase neuroinflammation which plays a significant role in degenerative diseases. Toxic substances including cytokines, tumor necrosis factors, glial activation are very harmful. Especially in the very early stages of the underlying disease, a vicious cycle of glial priming, release of pro-inflammatory factors and neuronal damage which influence the systemic inflammation[3,9,12] and contribute to reduce the intrinsic capacity of the central nervous system of progressive elimination of debris, then increasing the amount of amyloid between the neurons and interrupting connections and signal transmission. Functional disorganization of cerebral networks starts at a certain age, but this process may become pathological when a series of different mechanisms co-occur and interrupt the regular biochemical and neurochemical transmission. Symptoms of cognitive decline are not yet visible at this stage and this is the reason why the earliest disturbances remain often undiagnosed and un-mentioned.

The most common and prototypical clinical debut is a progressive, frustrating and embarrassing incapacity to form new memories, or to recall recently acquired verbal and non-verbal information. Names become very difficult to recall, faces are forgotten, places and roads appear inextricable. The progression is also predictable. Soon the patient becomes disoriented, displaces common objects, finds problems in organizing her/his life and becomes more confused, fatigued, irritable and forgets the meaning of words or finds difficult to manage money, familiar instruments, confuses day and night and even familiar faces. Language becomes scanty, non-fluent, confused and very poor of communicative information. Behavioral disturbances follow after a few years, agitation takes place and the patient is unable to autonomously live her/his life. This process may take almost 15-20 years before becomes clear, but once diagnosed, progression commonly takes its worst scenario within ten more years.

In the pre-dementia period, cognitive dysfunctions have a specific pattern. Episodic memory becomes faulty, object names are nor easily recallable, even name-face association of familiar people becomes a hard task. Handling more than two activities at once results very challenging and many errors appear in

conducting activities of daily life. Irritability becomes apparent and, at first, also depressive mood appears mixed with anxiety for the perceived incoming difficulties. After a few years though, especially if disturbed behavior is left undiagnosed, patients develop unawareness of their deficits, become fatuous and they loose insight into their own difficulties.

Cognitive testing has become the easiest and more requested valuation, often without significant results, early defective performance being "within normal limits"[8,14,18]. Neurological attention is seldom requested and more appropriate instrumental assessment is not given, loosing precious time and alternative treatment strategies. Basic CT scanning is not appropriate, MRI imaging is not specific and clinical interpretation assumes the style of "wait and see". After the 2007 criteria spread by Dubois and colleagues though, dementia in not an "exclusion diagnosis" but conversely an "inclusion diagnosis", that is, if cognitive disturbances surge to assume a significant impact on daily and working living, the first think we are forced is to pursue a "pattern of dementia"[6]. Still now though this is not the common approach. Diagnosis of dementia, preclinical or presenile, is not frequently made, often remaining in search of the "Alzheimer's pathognomonic findings.

Pathological Alzheimer's findings are also found in normal brain but these patients are not demented. Conversely patients diagnosed with "Alzheimer's disease very often do not show the pathological marks of the disease at autopsy. Alzheimer's disease has been conceived so far as a "*clinical-pathological construct*": if a person had amnestic symptoms they would have AD neuropathologic changes at autopsy; if the symptoms were absent, they would not have AD at autopsy. Cognitive dysfunction and disease became interchangeable[10]. Recently the most common construct to be utilized has been the "*clinical-biomarker*" approach[5,6], where biomarkers have been used to support and confirm a diagnosis of AD in symptomatic individuals. As a cognitive neurologist, one lesson I have learned in recent years is that amnestic multidomain dementia is neither sensitive nor specific for AD neuropathologic change, suggesting that cognitive disturbances and cognitive assessment can remain not an ideal way to investigate and define Alzheimer's disease.

Very recently, the National Institute on Aging-Alzheimer's Association set up a research framework[10] which is replacing our traditional knowledge and may serve as an updated guideline for clinical diagnostic procedures and therapeutic intervention. Although, they say, this a research framework not for clinical use, their conclusions are very strong and linear contributing to review our thoughts, diagnostic patterns and outcome consideration. The main contribution of this research paper could be summarized as follows:

1. We currently use the term Alzheimer's disease *indistinctly* to describe clinical syndromes that resemble the classical pattern of AD, but also to refer to the neuropathological hallmarks of the disease.
2. Disease-modifying substances being studied can only be applied in the very early (preclinical phase) of the disease; these individuals could not yet be labeled patients.
3. The disease once was confirmed only at autopsy. After 2011, with the advent of the biomarkers-approach, the disease could also be diagnosed reasonably well in the living brain.
4. To make a diagnosis of AD we must either perform a PET Amyloid or PET tau scan or (at least) quantify beta amyloid and/or tau in the CSF after lumbar puncture
5. Neurodegeneration, visible on MRI is not sufficient to enter the Alzheimer's spectrum, nor is a defective neuropsychological examination documenting multidomain areas of impairment, which could be not specifically related to other causes.
6. Biomarkers (either Imaging or cerebrospinal fluid) are a continuous measure of disease, which starts preclinically, before the symptoms start. Amyloid PET is a valid in vivo surrogate of the Abeta deposition in the brain, so is CSF Abeta 42 or the ratio Abeta 42/Abeta 40. The first biomarkers to become abnormal are those of Abeta.
7. There seems to be a causal upstream role for Abeta in the pathogenesis of AD. Amyloid biomarkers represent the earliest evidence of AD.
8. Both Abeta and pathologic tau biomarkers need to be present to apply the label of "Alzheimer's disease" in living individuals.
9. Neurodegenerative changes, both neuroradiological or neurocognitive, remain indicators of the severity and the progression of the disease; they cannot define the presence of the disease.
10. Cognitive performance then exists on a continuum and contribute to define categorical stages and progression of the disease, from a pre-clinical

AT (N) biomarker grouping
A = aggregated amyloid-beta or associated pathologic state
• CSF Abeta 42 or Abeta 42/Abeta 40 ratio • Amyloid PET
T = Tau pathology: aggregated tau (neurofibrillary tangles) or associated pathologic state
• CSF phosphorylated tau • Tau PET
(N) = Neurodegeneration or Neuronal injury. Not sufficient for "in vivo" pathologic definition of AD
• Anatomic MRI • FDG PET • CSF total tau

Table 1. Recent criteria: AT (N) biomarker grouping (*adapted from Jack et al., 2018*[10]).

phase of pauci-symptomatic or good aging to mild cognitive impairment, to early dementia, till the most severe stages of the disease. Even the most severe cases of dementia (clinical syndrome) may not be attributed to Alzheimer's pathology (non-Alzheimer's dementia).

This new paradigm of pathological definition of Alzheimer's disease greatly contributes to speak the same language between clinicians and researchers. It poses unquestionable clarity in the diagnostic process and relegates cognitive assessment to its role: a quantification of the relative cognitive devastation secondary to underlying degenerative pathology represented by AD, rather than a synonymous of AD. This paradigm makes light into the *neurobiology* of this common process linked primarily with aging (bad aging). This newly developed framework allows also a better patients' segmentation in clinical trials[4]. Biomarkers are invasive and expensive though and not easily implemented into our daily clinical activity. In the future we hope that other biomarkers could be available, less invasive and less expensive as well more at hand. But in the meantime every clinician needs to face a major problem, that is daily confrontation with the many questions of patients at their early symptomatic stage or their relatives who are first concerned for their dears but also make increasingly more questions about their future and the risk that they might develop of the same cognitive failures or the same disease. To their many questions indeed we have no answers, nor we can continue to use the answers available to us till a few months ago. Alzheimer's disease is a pathological process, which could be diagnosed "in vivo" following the specific and costly patterns of investigation as mentioned above. The shortcut of cognitive assessment and the lapidary diagnosis of Alzheimer's disease based on these results are no longer appropriate. Each of us need to clearly differentiate both clinically and discursively, the *neurodegeneration* responsible of the syndrome of dementia, illustrated on MRI or on cognitive evaluation, from Alzheimer's disease itself which needs to be ascertained with biomarkers, either on Imaging or with CSF findings.

□ FINAL REMARKS

Alzheimer's disease is a recently coined clinical-pathological entity, which was labeled after the work of Alois Alzheimer and his school more than a hundred years ago. For many decades it remained neglected, unknown, undiagnosed. By the end of the 20th century there was a surge of interest as a result of reduced mortality, better living and increasing "survival of civilized society". Pathological determinants of the disease were postulated and confirmed. Amyloid plaques and fibrillary tangles were discovered a hundred years earlier but the mechanisms of the neuronal degeneration, network disintegration, cognitive collapse and neuroimaging of the living brain made our clinical work more interesting and more incisive. Anticholinesterase medications came into the market and each of us cultivated the unconfessable certainty that a cure for the disease was soon arriving. After twenty and more

years of hope, of regenerated diagnostic criteria, of detailed guidelines, and of countless money investment in drug research, we must admit that a cure is not available. Biomarkers were emphasized in the living persons, which allowed us to make a step forward in understanding the early stages of the disease. However, we begin to understand that this "endemic" diagnosis is maybe the result of an increased survival of our society and the most "civilized " western (so far) populations. Centuries ago mortality reached astronomical numbers in the mid-ages: wars, pestilences, famines, childhood mortality, absence of surgical intervention, un-diagnosed diseases, etc. In current era childhood mortality is reduced significantly, youngsters survive even to the most dangerous and severe traumatic injury, surgical advancement has become impressive, late stage mortality due to vascular, inflammatory, neoplastic diseases have reached minimal terms. Survival is the norm. In the aging brain consequently neurodegeneration is a common finding and a frequent diagnosis. Neurodegeneration though is not synonymous of Alzheimer's disease and one more effort is due: correctly subdividing Alzheimer's disease from non-Alzheimer's pathology.

The last research effort by the group of Jack et al.[10] is in this direction. Now we need to get the most out of this "biomarkers' driven methodological diagnostic process". All the risk factors previously mentioned need to be explored and properly investigated, starting from the day of birth. Epigenetic factors are very crucial "starting" mechanisms of cognitive decline and dementing process[1]. However these environmental, life-related events and comorbidity causes may "trigger" and amplify what is already taking place, which is chronic inflammation, neurodegeneration and network disintegration of our once efficient brain.

The final last comment, from a clinical point of view remains the same: why do we make such refined taxonomies and diagnostic procedures to separate Alzheimer's from non-Alzheimer's pathology, if there is yet no medication available and there is no immediate future hope for any treatment of this *endemic result of "survival of the species"*?

To posterity the arduous sentence, said the poet. Or, "Posterity will judge".

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Disclosure. *The Author declare no conflicts of interest.*

Review

Frontotemporal dementia and related syndromes: a review

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SUMMARY: *Frontotemporal lobar degeneration is a clinically, pathologically and genetically heterogeneous group of disorders characterized by frontal and temporal lobes atrophy. Three major clinical syndromes are described: behavioural variant frontotemporal dementia, progressive non-fluent aphasia and semantic dementia. Patients with behavioural variant frontotemporal dementia present with changes in personality and behaviour such as disinhibition, apathy, loss of sympathy and empathy, compulsive behaviours, altered eating and drinking with sweet preference, hyperphagia and alcohol abuse. Neuroimaging shows frontal atrophy, hypometabolism and hypoperfusion. Semantic dementia is characterized by a prominent breakdown of semantic knowledge with fluent aphasia, single word comprehension deficit, associative agnosia and prosopoagnosia. Asymmetrical degeneration of the anterior temporal lobes is found. Patients with left-sided semantic dementia present with progressive fluent aphasia while patients with right-side atrophy usually have problems to recognize objects or familiar/famous persons. Patients with PNFA show effortful speech, impaired production with agrammatism and relatively preserved comprehension. PNFA is associated with atrophy, hypometabolism and hypoperfusion of the left perisylvian area. Overlap between the syndromes can occur, particularly later in the course. There is considerable heterogeneity in clinical presentations. Frontotemporal lobar degeneration may present with atypical parkinsonism such as corticobasal syndrome or progressive supranuclear palsy syndrome. Association with motor neurone disease is found. In the absence of definitive biomarkers, the diagnosis is dependent on clinical symptoms. Frontotemporal lobar degeneration is a pathologically heterogeneous spectrum of disorders. Three main histologies are described, involving tau, TDP-43 and FUS proteins. Principal gene mutations are found in the MAPT, GRN and C9orf72 genes. There is no available etiological therapy for frontotemporal lobar degeneration; symptomatic drugs and nonpharmacological intervention can help in management of symptoms.*

KEY WORDS: *Corticobasal syndrome, Frontotemporal dementia, Non fluent aphasia, Progressive aphasia, Progressive supranuclear palsy, Semantic dementia.*

INTRODUCTION

Frontotemporal dementia is an "umbrella" term that includes different clinical phenotypes due to FTLD[41]. The prototypic clinical picture is characterized by profound alteration in personality with behavioural changes associated to a dysexecutive syndrome that nowadays constitutes the bvFTD. Two clinical variants pertain to the domain of language. Semantic dementia is characterized by impairment of the semantic system with progressive aphasia and associative prosopoagnosia. Nonfluent progressive aphasia is characterized by a prominent non fluent aphasia with alteration of verbal production (anomias,

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Progress in Neuroscience 2019; 4 (1-4): 15-26. *ISSN: 2240-5127*
doi: 10.14588/PiN.2019.Luzzi.15

LIST OF ACRONYMS AND ABBREVIATIONS: **AD** = Alzheiemer's Disease; **ALS** = Amyotrophic Lateral Sclerosis; **bvFTD** = behavioral variant of FrontoTemporal Dementia; **bvFTD-PS** = behavioral variant of FrontoTemporal Dementia phenocopy syndrome; **CBS** = Corticobasal Syndrome; **CHMP2B** = CHarged Multivesicular body Protein 2B; **CSF** = CerebroSpinal Fluid; **EEG** = ElectroEncephaloGram; **FDG-PET** = FluoroDeoxyGlucose Positron Emission Tomography; **FTD** = frontotemporal dementia; **FTLD**= FrontoTemporal Lobar Degeneration; **FUS** = Fused in Sarcoma; **LBD** = Lewy Body Dementia; **lvPPA** = logopenic variant of Primary Progressive Aphasia; **MAPT** = Microtubule-Associated Protein Tau; **MND** = Motor Neuron Disease; **MRI** = Magnetic Resonance Imaging; **NFPA** = Nonfluent Progressive Aphasia; **nfvPPA** = non-fluent variant of Primary Progressive Aphasia; **PPA** = Primary Progressive Aphasia; **PRGN** = progranulin; **PSP** = Progressive Supranuclear Palsy; **SD** = Semantic Dementia; **svPPA** = semantic variant of Primary Progressive Aphasia; **TARDBP** = TAR DNA-binding protein; **TDP-43** = TAR DNA-binding protein 43; **VCP** = Valosin-Containing Protein.

phonological parahasias, agrammatism) and relatively spared comprehension. FTLD has a broad spectrum of clinical syndromes that include among the most frequent syndromes the corticobasal syndrome and progressive supranuclear palsy[1,3]. Association with motoneuron disorder is present[4].

Accurate diagnosis of patients in life is crucial, both on clinical and scientific grounds. From a clinical point of view it helps the patient and his caregiver to know the prognosis of the disease and it is of importance for optimal clinical care and management. From a scientific point of view it is crucial for clinical trials and genetic studies[14].

Distinct cognitive/behavioural syndromes reflect different topographical localization of pathology[45].

There is growing evidence that a comprehensive analysis of patients' clinical

history, neuropsychological profile, together with a full neurological examination, lead to a high degree of confidence in clinical diagnosis[45,47].

The present review aims to focus on the clinical spectrum of FTD to give a brief guide to the clinician to suspect and recognize FTD syndromes in the daily clinical routine.

Other aspects - epidemiology, genetics, pathology - will be briefly summarized.

□ HISTORICAL BACKGROUND

The first description of patients affected by FTD came from Arnold Pick[2] who described a series of subjects whose psychological and cognitive deficits were associated with a focal atrophy of the frontal and temporal lobes. After Pick description for most part of the last century focal atrophies included FTD have received little attention from neurologists, neuropsychologist and pathologists. The renewed attention came from the Manchester Group[41]. In 1992 J. Snowden described a clinical syndrome characterized by progressive fluent aphasia with alteration of semantics and loss of word meaning that she named "semantic dementia"[42].

The first diagnostic criteria for FTD have been formulated by the Lund and Manchester groups (the "Lund-Manchester criteria"[29,49]). Three clinical syndromes were identified and criteria for each syndrome were provided: frontemporal dementia characterized by prominent behavioural symptoms, semantic dementia characterized by semantic memory breakdown and primary nonfluet aphasia characterized by altered language production. Recently, the International Behaviouaral Variant FTD Criteria Consortium developed revised guidelines for the diagnosis of bvFTD[35]. The two language variants have been reclassified within the primary progressive aphasias where semantic dementia constitutes the svPPA and the NFPA constitutes the "nonfluet variant" of PPA[10].

□ EPIDEMIOLOGY

Frontotemporal lobe degeneration is considered the third most common cause of dementia, after Alzheimer's disease and dementia with Lewy bodies. Frontotemporal lobe degeneration incidence is estimated between 1.61 and 4.1 cases per 100.000 people/year and prevalence about 10.8/100.000 people, with the highest prevalence reached between 65 and 69 years of age[15,30].

Clinic-based studies in dementia hypothesise that FTLD is responsible of about 5% of all cases of degenerative cognitive impairment, in particular presenile dementia.

Frontotemporal lobe degeneration is the most common cause of dementia of degenerative origin below 65 years of age, despite in the literature have been described some cases with age of onset included between 30 and 90 years.

Frontotemporal lobe degeneration mean age at onset is about 60 years[15].

Among all dementias, FTLD is the form with the most rapid clinical progression: the time between cognitive symptoms onset and death is variable from a minimum of 6 years and a maximum of 10 years approximately. In particular, the fastest progression has been documented in the behavioural variant of frontotemporal dementia[15].
In frontotemporal lobar degeneration there are no sex differences.
bvFTD is the most common variant, comprising about half of patients. Within the progressive primary aphasias the non-fluent variant is the most frequent[15].

□ BEHAVIOURAL VARIANT OF FRONTOTEMPORAL DEMENTIA

❐ Clinical features

The behavioural variant is characterized by personality changes and alteration in personal and social behaviour. The onset of symptoms is usually insidious. Loss of social awareness and insight is quite common and it is reported by the patient' relatives as a "reduction of courtesy" or "loss of manners". The patient is often referred as "less polite" with visitors and commits false steps in social life without concern. Relatives usually describe the patients as "instinctive", "primitive" as they notice that the patient progressively tends to "obey to instinctual behaviour" avoiding to respect the social context[32].
Changes are typically noticed in the personal hygiene. The patients avoid contact with water or avoid to change their clothes and do not show interest in their physical appearance[49].
Dressing is usually reported as bizarre (winter clothes during the summer or vice versa). Women may show alteration in applying make-up (they can stop to apply make-up or by contrast can use garish make-up); details in dressing are usually omitted (shoes unlaced, fasteners unclosed, blouses unbuttoned)[41].
Altered eating and drinking are very common. Patients may over-eat with tendency to eat sweet foods. Typically the relatives notice that the patient has lost the capacity to "stop eating" and it is frequently reported that the patient can eat huge amount of food (cakes, biscuits, piece of butter etc). Selective food fads can be present. Less frequent is the tendency to eat inedible objects or fluids (e.g. soap) often due to the presence of semantic breakdown (the patient mistakes a white fluid for something edible such as milk)[33].
Loss of empathy or sympathy is very frequent as well. Affective symptoms vary from fatuous jocularity to emotional indifference and shallowness. The patients can be described by relatives as "emotionless" and they do not show interest for autobiographical events or social events highly emotive. By contrast, they can be "over-emotive" and show an inappropriate and exaggerate emotional reaction[34,46].
Psychosis is not very frequent in bvFTD phenotype. A powerful association between C9ORF72 mutations and psychosis is reported. In these patients behavioural characteristics are qualitatively distinct with presence of with paranoid, deluded or irrational thinking[16,44].
Sphincter control may be altered from the early stage with not criticised incontinence. Sexual alterations can be present as well, even they are not very frequent. The patients can show increased sexual demand to the partner as part of their behavioural disinhibition or loss of libido and sexual indifference (more frequent in apatethic patients)[41].
Motor behaviour varies from akinesia in apatethic patients (they usually tend to sit on a chair or on the sofa without any movement) to wandering behaviour or presence of repetitive movements[41]. Perseverations and behavioural stereotypies can take a variety of forms, from simple repetitive movements (e.g. rubbing hands) to obsessive-compulsive behaviour with rituals and can assume the form of utilization behaviour. In this last case the patient's attention is captured by objects within his reach that are grasped by the patient and used (e.g. if a bottle of water is on the table next to the patient, he can picks up and drinks from the bottle several times). This un-controlled behaviour can sometime be responsible of over-eating (when the food is in front of the patient he will eat the food until t is not finished)[33,34,41].
Even if the patient does not show primary language deficits the quality of speech is altered. Usually economy of speech is frequent especially in the moderate and severe stages (within the so called "akinetic mutism"). Typically the patient does not initiate conversation and can avoid to answer to the questions of the examiner. Laconic speech is frequent with minimal sentences with a single or few words ("yes", "no" "I don't know"). Echolalia can be present ("How are you?" -"How am I?"; "Where are you from?" -"Where am I from?"). Verbal stereo-

typies are frequently noted and are part of a stereotyped behaviour[35,41,49].

❒ Neurology

bvFTD patients are typically physically well and they do not show neurological signs. In some cases, clinical sign of striatal involvement can be present with akinetic extrapyramidal syndrome. Ataxia is not present. Early primitive reflexes (e.g. grasping, sucking etc.) can be present. Incontinence can be an early sign; typically the patient does not criticize incontinence[35,41].

❒ Neuropsychology

Frontal-dysexecutive syndrome is invariably present in bvFTD. Anyway, especially in the early stage an accurate and detailed evaluation of cognitive functions, in particular the ones pertaining to the frontal lobe, should be carried out, because a very mild bvFTD patient could not show problems in most domains and not invariably all executive functions could be impaired. In the more advanced stages the dysexecutive syndrome with poor attention, abstraction, planning and verification of activities can be responsible of poor performance in several cognitive domains such as memory, calculation, spatial skills, language. Neuropsychological examination should be carried out in these patients by an expert neuropsychologist to avoid judgement bias (very mild FTD with subtle frontal syndrome can be interpreted as normal subjects, while moderate-severe FTD patients can be interpreted as Alzheimer's disease cause of the overall bad performance in several tasks)[14,29,35,41,49].
The examination of "quality" of errors committed and the patient's behaviour during the cognitive examination can be of help (perseverations, stereotypies, concreteness of thought, absence of mental effort, wandering or utilization behaviour etc.)[5].

❒ Investigations

Neuroimaging can help clinicians in making differential diagnosis. MRI scan shows bilateral frontal atrophy with possible involvement of anterior temporal lobes. Usually, posterior cortex is spared.
MRI scan can also contribute to exclude other potential causes of frontal lobe syndrome such as brain tumours, vascular encephalopathy, normal pressure hydrocephalus[7].
FDG-PET may be more sensitive than MRI in the early stages of disease and reveals a decrease metabolism in frontal, anterior cingulate and anterior temporal regions[7].
EEG is normal in bvFTD[29,41,49].
CSF examination may reveal high levels of tau and phospho-tau with beta amyloid in the normal range[39].
Laboratory exams can help to exclude hypothyroidism, syphilis, cobalamine deficiency.

❒ Differential diagnosis

Within the chapter of neurodegenerative brain diseases differential diagnosis includes Alzheimer's disease and less frequently Lewy body dementia[18,38,45].
Memory loss constitutes the prototypical presentation of Alzheimer's disease. Even FTD patients can be described by their relatives as "forgetful". Anyway, memory problem is not the dominating feature and it is usually reported to vary according the different contexts and situations. The "frontal variant" of Alzheimer's disease may be difficult to distinguish from FTD. Usually, frontal syndrome is present from the early stages in patients with familiar AD. In these cases a deep neuropsychological examination together with neuroimaging and biomarkers can help in differential diagnosis[38,41,45].
Clinical presentation of Lewy body dementia is usually very different from FTD and the presence of cognitive decline, together with extrapiramidal signs, fluctuation of symptoms, delusions and hallucinations can orient toward LBD. Hallucinations have been described also in FTD and when present can be confounding. Hallucinations are reported to be present in patients carrying C9ORF72 mutation. Cognitive assessment can help in differential diagnosis. In LBD neuropsychological evaluation reveals visuoperceptual and spatial prominent alterations (usually absent in FTD) together with a dysexecutive syndrome and a variable and usually mild involvement of memory[38,41].
bvFTD can start with indiscriminate over-drinking leading the clinician to impute the cognitive symptoms to excessive alcohol intake. Anyway, a careful history can contribute to rule out alcoholism. Even if frontal lobe syndrome and amnesia are

typical of both patients suffering from chronic alcoholism and from Wernicke-Korsakoff symdrome, patients with FTD do not show the classical neurological complications (e.g. cerebellar syndrome, peripheral neuropathy), neither shows the systemic effects (e.g. epatopathy)[41].

The behavioural alterations, with apathy, personality changes, obsessive compulsive behaviour, can be interpreted as part of a psychic disorder.

Especially in the early stage, the bvFTD patient can perform well neuropsychological tests and this can reinforce the diagnosis of "non-organic" disorder. Furthermore, the presence of familiar history (presence of "psychiatric disorders" in other family members with institutionalisation) can reinforce the idea of a psychic disorder. In the clinical routine it is quite common that bvFTD are referred to a memory clinic from psychiatrists after several pharmacological attempts without clinical benefit[18].

Traumatic encephalopathy frequently leads to damage of the frontal lobes and behavioural alterations can be persistent. Anyway, the temporal coincidence with the head trauma and development of behavioural symptoms, together with the patient's follow-up (absence of progressive decline of performance) can help in differential diagnosis[41].

Syphilis can mimic the presence of a bvFTD because often the patient tends to manifest behavioural problems such as disinhibition, hyperphagia, wandering behaviour.

Within the differential diagnosis of bvFTD the clinician should consider the bvFTD-PS. This is a well-documented syndrome in which the patient who manifests typical signs and symptoms of bvFTD do not show clear biomarker evidence of FTLD. These patients do not clearly demonstrate progressive clinical deterioration[17]. Usually these patients suffer from a psychiatric disorder. Anyway, very slowly progressive forms of bvFTD, with disease duration upwards of 20 years have been described[18,48].

☐ SEMANTIC DEMENTIA/ SEMANTIC VARIANT OF PRIMARY PROGRESSIVE APHASIA

❐ Clinical features

Semantic dementia is one of the two clinical variants that impair language[13,41,49]. Although SD is currently reclassified within the primary progressive aphasias, the language disorder is only one of the clinical equivalents of the disease that primarily concerns an alteration of the semantic system. Therefore, if it is true that in most cases the patient manifests a language disorder, it does not represent the only cognitive alteration and often the patients may exhibit an associative prosopagnosia.

SD is more properly the clinical correlate of an alteration of the semantic system, a wide and complex brain network that stores and processes all aspects relative to word knowledge[41]. The semantic system is mainly localized within the temporal cortex (temporal poles and middle and inferior temporal gyris) and because the degenerative process is confined to these regions of the brain, the clinical syndrome pertains to a multimodal breakdown of meaning. Left temporal cortex is mainly implicated in linguistic aspects of word knowledge, while the non verbal equivalents are mainly processed by the right temporal lobe. It follows that, depending on the left or right prevalence of the degenerative process, the patient can manifest primarily language disorders or an associative agnosia and prosopagnosia, respectively[8,19].

The designation of semantic variant of primary progressive aphasia reflects the predominance of the language problems that are apparent to the clinician, as the alterations of language are easily detected by the patient's family and by the clinician during the visit[13,41].

However, the disorder is usually not confined only to the verbal domain and problems in recognise objects and faces are often present[8,19].

Language alterations are the hallmark features of the svPPA and they are usually characterized by anomies and semantic paraphasias. The patient substitutes a semantically related alternative for the correct word, i.e. pertaining to the same category of the target word ("cat" instead of "dog", "fork" instead of "spoon"). Phonemic paraphasies (sound based errors) are never reported. Word comprehension is altered, especially in the moderate to severe stages of the disease. Language is fluent and often garrulous without detectable syntactic errors[13,36,41,49].

Loss of meaning can involve objects, faces, and voices. The patient can therefore manifest problems in recognizing objects and familiar faces or famous persons[8,13,19,41].

Behavioural problems are not very frequent. When present, alterations in behaviour are qualitatively distinct from the behavioural changes of bvFTD with

prevalence of compulsive and stereotypic traits, loss of awareness of danger, preference for fixed routine (e.g. clock-watching), inappropriate preoccupations. Parsimony is frequent and the patient avoids spend money and tends to limit expenses by buying low-cost products (food, clothes, shoes, etc.). Unlike the bvFTD where there is indiscriminate hyperphagia, patients with SD tend to eat a narrow range of foods[13,41,49].

❒ Neurology

Neurological examination is normal. Articulation and prosody are intact. Only in the advanced stages of the disease can appear primitive reflexes, frontal signs or akinetic extrapiramidal syndrome[41].

❒ Neuropsychology

Neuropsychological examination can be of extreme value to corroborate the diagnosis of semantic dementia. Neuropsychological findings are highly characteristic and uniform and consist of an almost selective impairment of semantic tasks that involve both the verbal and non verbal aspects. Language is fluent and effortless. Some pauses can be due to anomies. Semantic paraphasies are often present and the patient tends to use broad generic terms (e.g. "thing"). Semantic fluency is very poor[36]). Syntax is preserved. No phonological errors are detected. Tasks exploring comprehension reveal altered single word comprehension, with a characteristic "word frequency effect", where common words (high frequency words - e.g. "cat") are better understood than unusual words (low-frequency words - e.g. "penguin"). Reading and writing are fluent, but regularization errors are often present due to surface dyslexia and surface dysgraphia respectively[14,41,49].
Object recognition difficulties are often present in SD. Typically the patient tend to recognize better common objects used in the day-to-day life than unusual objects. For example, the patient can recognize and use his shaving razor without problems, but is unable to recognize a new razor purchased at the supermarket. Similarly, the patient may not recognize known faces or famous personalities[8,19]. Usually the faces of family members (high frequency stimuli) are recognized until the advanced stages of the disease.
Autobiographical memory is preserved and patients have no difficulties to remember facts, appointments and episodes of their life[41,47].
Calculation and reckon change is usually preserved[21].
They do not show neither spatial nor visuoperceptual problems and they do not get lost in the environment. They can drive on known routes until the late stages of the disease without get lost and the main problem they can manifest is the inability to recognize road signs[20].

❒ Investigations

Traditional neuroimaging (CT scan or MRI scan) is usually helpful in diagnosis because it shows a selective atrophy of temporal lobes extending mainly to the temporal pole and inferior and middle convolutions. Atrophy is clearly asymmetric in the two hemispheres. The degree of asymmetry is usually proportional to the phenotypic expression of the disease, with a prevalent language disturbance in predominantly left atrophy and conversely a prominent associative agnosia and prosopoagnosia in patients with predominantly right brain atrophy[29,35,49].
FDG-PET show hypometabolisms in the anterior temporal lobes and can reveal alterations in the mild stage of the disease when the mild atrophy is not necessarily detectable by the structural brain imaging[7].
EEG is normal. CSF examination may reveal high titres of tau and phospho-tau with normal levels of beta-amyloid[39].

❒ Differential diagnosis

In the first instance SD should be differentiated from the other two variants of primary progressive aphasia(10).
Usually an expert neuropsychologist in language disorders can help the clinician because the neuropsychological pattern of SD is characteristic and the features of the language disorder are easily differentiated from the pattern of NFPA and lvPPA. The main aspects that allow to make the diagnosis are the presence of semantic breakdown without neither orthographic nor syntactic errors and single-word comprehension deficit with a spared verbal working memory[10].
Semantic dementia should also be differentiated from

Alzheimer's disease. The absence of prominent amnestic syndrome, the absence of visuospatial symptoms makes reasonably easy the diagnosis[15,41].
A very similar clinical picture to that of semantic dementia is appreciable in herpetic encephalitis that is characterized by the presence of a fluent aphasia with main impairment of the lexico-semantic level. Anyway, the temporal trend (abrupt or subacute onset of symptoms in herpetic encephalitis) and the clinical spectrum of related symptoms and signs (fever, headache, etc.) allow to rule out this disease without problems[41]. In rare cases Creutzfeld-Jakob disease can contemplate the presence of aphasic syndrome but the temporal trend and constellation of other neurological signs (cerebellar syndrome, cortical blindness, etc.) helps the clinician to make the correct diagnosis.
SD in one of the clinical syndrome more difficult to appreciate and recognize especially in the mild stage of disease, where other cognitive domains except semantics are spared and the patient is reported to be completely autonomous in the daily routine. Usually the patient is dismissed as "normal" or may be misdiagnosed as suffering from psychic disorder[41].

□ PROGRESSIVE NON-FLUENT APHASIA/ NON-FLUENT VARIANT OF PRIMARY PROGRESSIVE APHASIA

❒ Clinical features

PNFA, now relabelled as the non-fluent variant of PPA, is characterized by a selective disorder of language. Patients usually show a long history of slow and insidious trouble in speech production in contrast to spared speech comprehension. The patient come to the attention of the neurologist because notes errors both in oral and written language. Errors in writing may precede alteration in speech production of several years[11,12,26]. Typically the patient has good insight and can describe his symptoms carefully. Phonemic paraphasias are frequent and the patient refers that he makes errors in "pronunciation". Vowels and consonant may be altered ("car" → "bar") with deletions, substitution, insertions, and duplications. At the beginning of the disease language may have a stuttering quality due to multiple attempts to pronounce the right word and try to correct the paraphasias. During the course of the disease oral and written language becomes more and more telegraphic and assumes the form of "agrammatism" where all functions, such as prepositions, articles, adverbs are omitted[11,12,29,41,49].
Speech apraxia may be present and is usually mistaken for dysartria. Speech apraxia reveals its linguistic (and not merely articulatory) form in relation to the type of speech output of the patient. Typically speech apraxia varies as a function of the orthographic complexity of the word pronounced and may "disappear" in recitation of verbal series[10,11,12,41].
Other cognitive functions are usually spared in the mild to moderate stage and both patient and relatives do not refer problem in day-to-day memory or spatial orientation. Usually frank behavioural symptoms are absent, even they can arise during the course of the disease. Patients can be relatively independent in their routine functioning until the severe stages of the disease[10,41,49].

❒ Neurology

Usually neurological examination is within the normal range. A mild to moderate rigid-akinetic extrapyramidal syndrome may be present[41,49].

❒ Neuropsychology

Neuropsychological examination reveals a selective impairment of language in absence of a diffuse cognitive decline. Language is agrammatic and hesitant. Phonemic errors can be detected in oral and written language. Repetition is altered as well. Lexical comprehension is relatively preserved. Memory is usually normal. Non verbal memory should be preferred as the performance in verbal memory tests is invariably altered cause of the language problem. Episodic memory is normal. Visuoperception and spatial skills are preserved as well[10,12].
Mild to moderate (according to the stage) dysexecutive syndrome can be present[12].

❒ Investigations

Structural neuroimaging (CT scan or MRI scan) reveals asymmetric left perisylvian atrophy and conversely FDG-PET shows hypometabolism in the same regions[7,11,12].
EEG is usually normal[10,49]. CSF examination shows similar findings of bvFTD[39].

❒ Differential diagnosis

The differential diagnosis of NFPA primarily relates to other forms of progressive aphasia[10].
Detailed language assessment provides considerable help to the clinician[10,12].
NFPA is characterized by agrammatism, presence of speech apraxia and phonological paraphasias. Semantic domain is usually spared and single word comprehension is within the normal range.
NFPA is now counted among the phenotypic variant of corticobasal degeneration (*see below*). The presence of neurological sign (often extrapiramidal signs such as limb apraxia, unbalance etc) can be of help in the differential diagnosis[1,3].
The cognitive findings of NFPA are very similar to the Broca's aphasia a common presentation of left anterior strokes. Anyway the abrupt onset of symptoms typical of stroke allows to make a differential diagnosis without problems[41].

□ OVERLAPPING SYNDROMES

Phenotypic presentation of the frontotemporal lobar degeneration is heterogeneous.
In several cases patients demonstrate variable mixtures of symptoms and sign pertaining to progressive supranuclear palsy syndrome, corticobasal syndrome and motor neuron disease[1,3].
The association between FTD and MND is well established[4,44]. Patients presenting with FTD may develop MND and patients with MND may develop FTD[9].
The association between FTD and MND is frequent in subjects carrying C9ORF72 mutation[44]. Distinct clinical characteristic have been described in these patients[31,44].

□ ATYPICAL PHENOTYPES IN FRONTOTEMPORAL LOBAR DEGENERATION

Due to the focal onset and the slow progression of degeneration, in some cases unusual cognitive profiles can be observed where a single domain is compromised in the absence of other canonical signs of the disease[41]. We described a case of a woman presenting with a two-year history of selective FAS in absence of other neuropsychological signs[27] and a patient who showed a seven-year history of slowly progressive pure dysgraphia[26].
Unusual associations of syndromes pertaining to FTLD have been described[41]. We reported two cases of patients showing both the features of semantic dementia and corticobasal syndrome[22,24]. A similar case was described by Clerc et al.[6] with autoptical evidence of 4R tauopathy.

□ GENETICS

Frontotemporal lobar degeneration has a marked component of familiarity: in about 17-43% of affected individuals there is a familiarity for a similar disorder[9].
Currently, the rate of familiarity seems underestimated even because of the frequent difficulty to perform an exhaustive family history.
In FTLD causal genetic mutations are often reported in apparently non-familiar cases. This phenomenon is probably attributable to several factors: the occurrence of a new mutation, an incomplete penetrance or an unrecognised familiarity (for example, due to families deaths at an early age).
Recruitment of large cohorts of familiar cases of FTLD and actual genome sequencing technology are significantly increasing about the genetic basis of familiar FRTL.
About 40-50% of familiar FTLD cases are explained by causal mutations of known causative genes but the remaining familiar cases causative mutation has not been discovered yet.
The genetic forms of FTLD represent a substantial percentage variable from 25 to 50%; in most cases the transmission is attributable to an autosomal-dominant pattern, with extremely variable clinical phenotype[37]. The first genetic mutation responsible for FTLD to be detected was in the MAPT gene (which encodes the associated microtubular protein), located on chromosome 17 (17q21) and coding the tau protein, estimated as responsible for 10-20% about all cases of familial FTLD[40]. Since 1998, about 44 different mutations have been identified in 132 different families of this gene, which seem globally responsible for 5-20% of familiar FTLD. In 2006, PRGN gene was identified on chromosome 17. In following years, about 70 different mutations of this gene were discovered in 199 families affected by FTLD, responsible of about 6-10% of cases of familial cases[23,43]. Recently, C9orf72 gene involved

in FTLD has been identified, located on chromosome 9. Its mutation seems not only related to the FTD/MND (motoneuron disease) phenotype, but it also appears to be the most frequently documented in the familial forms of FTLD (11.7% of cases) and in familial amyotrophic Lateral Sclerosis (23.5% of cases)[25,28,40].

Less common mutations (found in about 1% of cases of familial frontotemporal lobe degeneration), refer to other genes such as VCP, CHMP2B and TARDBP[40].

□ PATAHOLOGY

From a macroscopic point of view, the FTLD is characterized by frontal and temporal lobes atrophy; in particular, at least at the onset, this atrophy appears to be confined at the level of the anterior cingulate cortex, the fronto-insular regions and the lateral orbit-frontal cortex. As the pathology progresses, atrophy also tends to spread to the dorsolateral prefrontal cortex and to the anterior and posterior portions of the temporal lobes. In the case of nfvPPA, anterior atrophy of the lower left and insula frontal atrophy occurs, while in the svPPA the first brain area to be involved is the anterior portion of the left temporal lobe (initially the antero-inferior portion and only later the posterior one), then the contralateral analogous area, the posterior insula and the ventro-medial frontal lobe are involved[18,28,41].

From the histological point of view the first protein recognized having a role in FTLD was the tau protein (FTLD-tau). Tau protein is encoded by a gene composed by 16 exons in chromosome 17 and the central nervous system isoforms are generated by alternative RNA splicing of their exons. This protein, involved in axonal transmission, in FTLD is hyperphosphorylated and present as aggregates in a series of pathologies consequently defined taupathies, which include AD, Pick's disease, cortical-basal degeneration and progressive supranuclear paralysis. Neuronal tau deposit included pretangles, neuro-fibrillary tangles and Pick bodies. These histological finding are not documented in all cases of frontotemporal lobe degeneration, but only in a small number of them[18,28].

Another histological marker present in about half of patients with frontotemporal lobe degeneration is ubiquitin, present in the form of intracellular inclusions. Only a decade ago was identified the TDP-43. TDP-43 is a RNA-binding domain protein involved in multiple cellular processes and it is the most important component of tau-negative, ubiquitine-positive intracellular inclusion in frontotemporal lobe degeneration[16,28].

Another protein found to be present as intracellular inclusions is the FUS protein, another RNA-binding protein[28].

FUS protein is a RNA-binding protein. In ALS and FTLD brain tissues, FUS and TDP-43 result partially lost from the nucleus in neuron and glia and aggregate in cytoplasm and, less frequently, in the nucleus[28].

TDP-43 and FUS are nuclear carrier proteins that have a role in RNA metabolism regulation, whereas tau protein (a MAPT product) is involved in intracellular transport, in particular microtubules assembly/disassembly[16,28].

Histologically, FTLD is characterized by the accumulation at the cellular level of aggregated abnormal proteins of neuronal and glial origin. In 45% of the cases approximately, intracytoplasmic neuronal inclusions are formed by microtubule associated protein tau (FTLD-tau). Round bodies (Pick bodies) and glial inclusions of the tau protein coexist in about half of the intracellular tau-positive forms. About 50% of FTLD cases are characterized by the presence of neuronal intracytoplasmic inclusion and neuronal intranuclear inclusion formed by TDP-43 protein (a RNA and DNA binding protein). These forms are called FTLD-TDP. The remaining 5% of cases the neuronal intracytoplasmic and neuronal inclusion are characterized by the FUS protein, and are called FTLD-FUS[16,28].

□ TREATMENT

Until now there are not approved treatments to manage FTD syndromes. Cholinesterase inhibitors and memantine have not demonstrated clinically significant efficacy in treating FTD patients[50].

Symptomatic drugs can have some benefit on behavioural symptoms. SSRI treatment has some benefit on eating, agitation, irritability, dysphoria, and depression. Antipsychotics have been used to treat agitation and psychosis although the presence of side effect limits their utilization[50].

Nonpharmacological interventions and caregiver support can help to improve symptoms in FTLD[50].

Although recent advances suggest potential novel

therapeutic targets, data concerning their effectiveness are still preliminary or preclinical. Further studies are required to develop pharmacological interventions[50].

□ CONCLUSION

The purpose of the present review was to describe the clinical features of the variegated phenotypic spectrum of FTLD in order to provide a practical aid to the clinician to make a correct diagnosis.
FTLD is a heterogeneous group of disorders characterized by disturbances of behaviour and personality and different types of language impairment associated to atrophy of the frontal and anterior temporal lobes.
Together with the three more frequent syndromes (bvFTD, SD and NFPA) there is a significant clinical, pathological and genetic overlap between FTD and motor neuron disease/amyotrophic lateral sclerosis and the atypical parkinsonian syndromes, such as PSP and CBS.
The clinical history together with the neuropsychological evaluation provides fundamental information for the diagnosis of the different clinical variants. Instrumental examinations as well as genetics are helpful for a correct diagnostic classification.

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Disclosure. *There are no actual or potential conflicts of interest with any author of this paper.*

Review

Lewy body dementia

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SUMMARY: *Dementia with Lewy bodies represents the second most common cause of neurodegenerative dementia after Alzheimer's disease. The Dementia with Lewy Bodies Consortium has refined its recommendations about the clinical and pathologic diagnosis of dementia with Lewy bodies, updating the previous report, which has been in widespread use for the last decade. The revised dementia with Lewy bodies consensus criteria now distinguish clearly between clinical features and diagnostic biomarkers, and give guidance about optimal methods to establish and interpret these. Important new information has been updated about previously reported aspects of dementia with Lewy bodies, with increased diagnostic weighting given to REM sleep behavior disorder and ^{123}iodine-metaiodobenzylguanidine myocardial scintigraphy. The diagnostic role of other neuroimaging, electrophysiological, and laboratory investigations is also better specified. Substantial progress has been made since the previous report in the detection and recognition of dementia with Lewy bodies as a common and important clinical disorder.*

KEY WORDS: *Biomarkers, Consensus criteria, Dementia with Lewy bodies, EEG abnormalities, Magnetic resonance imaging studies, Treatment options.*

OVERVIEW

Dementia with Lewy bodies is the second most common form of neurodegenerative dementia after Alzheimer's disease.

DLB tends to be underdiagnosed during life and mostly misdiagnosed as AD, due to clinical overlap between the two diseases.

It is important, however, to differentiate between these two forms of dementia since the earliest stages because, compared to patients with AD, those with DLB may be considerably more sensitive to adverse effects of neuroleptics[5] and may exhibit faster disease progression[45] and different response to ChEIs[30]. To reach a satisfactorily accuracy of the diagnosis of DLB, great emphasis has been placed on methods evaluating the uptake of either DAT in basal ganglia[44,52] or MIBG in the myocardium[54]. These methods, respectively exploring the integrity of the nigrostriatal dopaminergic system and of postganglionic sympathetic cardiac innervation, have been suggested to improve clinical diagnostic accuracy of DLB, but there is a clear need of other biomarkers to assist with accurate identification of this entity.

Cognitively, DLB patients can display marked deficits in executive and visuo-visuo/spatial-perceptual function, as well as marked variations in their level of arousal and attention, which are typically known as cognitive fluctuations[29,39,40,42]. Clinical features associated with DLB also include spontaneous motor

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Progress in Neuroscience 2019; 4 (1-4): 27-32.
ISSN: 2240-5127
doi: 10.14588/PiN.2019.Bonanni.27

LIST OF ACRONYMS AND ABBREVIATIONS: **^{123}I-FP-CIT** = [^{123}I]-N-(3-FluoroPropyl)-2-Carbomethoxy-3-(4-Iodophenyl) norTropane; **AD** = Alzheimer's disease; **ChEIs** = CholinEsterase Inhibitors; **CIS** = Cingulate Island Sign; **DAT** = Dopamine Transporter; **DLB** = Dementia with Lewy bodies; **DTI** = Diffusion Tensor Imaging; **EEG** = ElectroEncephaloGram; **GM** = Grey Matter; **FDG-PET** = Fluoro-Dexosi-Glucose Positron Emission Tomography; **GM** = Gray Matter; **MIBG** = MetaIodoBenzylGuanidine; **MMSE** = Mini-Mental State Examination; **MRI** = Magnetic Resonance Imaging; **NAA/tCr** = N-Acetylaspartate/Total Creatine; **PSG** = PolySomnoGraphy; **RBD** = Rapid eye movement sleep Behavior Disorder; **REM** = Rapid Eye Movement; **tCho/tCr** = total Cholines/tCr = total creatines; **SPECT** = Single Photon Emission Computed Tomography.

features of parkinsonism[39], but it is the non-motor manifestations including visual hallucinations, autonomic dysfunction, syncope, repeated falls, REM sleep behaviour disorder, delusions and depression, to represent the most disruptive symptoms for patients and their caregivers[39].

There are also a number of treatment challenges. CHEIs may produce substantial reduction in apathy and improve visual hallucinations and delusions in DLB[40]. The use of antipsychotics for the acute management of substantial behavioral disturbance, delusions, or visual hallucinations comes with attendant mortality risks in patients with dementia, and particularly in the case of DLB they should be avoided whenever possible, given the increased risk of a serious sensitivity reaction[36,42]. Low-dose quetiapine may be relatively safer[34] than other antipsychotics and is widely used. There is a positive evidence base for clozapine in PD psychosis, but efficacy and tolerability in DLB have not been established. Newer drugs targeting the serotonergic system, such as pimavanserin[15], may be alternatives, but controlled clinical trial data in DLB are needed. Although depressive symptoms are common in DLB, trial data are insufficient.

DLB patients may benefit from levodopa preparations introduced at low doses and increased slowly to the minimum required to minimize motor disability without exacerbating psychiatric symptoms[25,41].

The Dementia with Lewy Bodies Consortium has refined its recommendations about the clinical and pathologic diagnosis of DLB. The revised DLB consensus criteria now distinguish clearly between clinical features and diagnostic biomarkers.

Important new information has been updated about previously reported aspects of DLB, with increased diagnostic weighting given to REM sleep behavior disorder. The diagnostic role of other neuroimaging, electrophysiological, and laboratory investigations is also better specified. Substantial progress has been made since the previous report in the detection and recognition of DLB as a common and important clinical disorder. During that period DLB has been incorporated as a separate nosological entity into DSM-5, as major neurocognitive disorder with Lewy bodies. 'There remains a pressing need to understand the underlying neurobiology and pathophysiology of DLB, to develop and deliver clinical trials with both symptomatic and disease-modifying agents, and to help patients and carers worldwide to inform themselves about the disease, its prognosis, best available treatments, ongoing research, and how to get adequate support'.

A collection of studies have been recently performed in order to define possible specific pathophysiological mechanisms underlying the appearance of specific clinical features of DLB, with the double aim to explain clinical presentation and potentially to provide possible diagnostic markers of disease[38].

In the present chapter we will summarize the main results of studies focused on DLB biomarkers and we will underline the significance of each of these biomarkers in terms of diagnostic accuracy and of pathophysiological mechanisms. Biomarkers will be divided in two sections, as suggested by the last Consensus document[38]: Indicative and supportive biomarkers. Major emphasis will be given to EEG and MRI studies which are the main fields of contributions by the authors.

□ INDICATIVE BIOMARKERS

■ **SPECT-DAT SCAN.** The functional integrity of dopaminergic nigrostriatal pathway can be studied with SPECT imaging by using ligands of presynaptic DAT, such as ^{123}I-FP-CIT. A reduction of SPECT ligand binding to DAT correlates with the loss of presynaptic dopamine. The rationale supporting the use of ^{123}I-FP-CIT SPECT as a supportive tool in the diagnosis of DLB is represented by the pathological peculiarities of DLB, characterized by abnormal inclusion bodies (Lewy bodies) in limbic, neocortical and brainstem areas with concomitant nigrostriatal degeneration

and loss of pre-synaptic dopamine transporters in the striatum[37,53]. For these reasons, low dopamine transporter uptake in basal ganglia on ^{123}I-FP-CIT SPECT has been listed as an indicative biomarker of DLB in the international consensus criteria for the diagnosis[38,55].

- **META-IODO-BENZYL-GUANIDINE.** Reduced uptake on metaiodobenzylguanidine myocardial scintigraphy. ^{123}Iodine-MIBG myocardial scintigraphy quantifies postganglionic sympathetic cardiac innervation, which is reduced in DLB[43,51]. Useful sensitivity (69%) and specificity (87%) values for discriminating probable DLB from probable AD rise to 77% and 94% in milder cases (MMSE > 21). MIBG imaging was already described in the supportive feature section of the previous version of the Consortium on DLB Guidelines[39]. According to this report, delayed MIBG images resulted in highly reliable differentiation of DLB from AD with both the sensitivity and the specificity being 100%, regardless of the presence or absence of parkinsonism[55].
- **POLYSOMNOGRAPHY CONFIRMATION OF REM SLEEP WITHOUT ATONIA**. PSG demonstration of REM sleep without atonia[22,35] is a highly specific predictor of Lewy-related pathology. If the PSG shows REM sleep without atonia in a person with dementia and a history of RBD, there is a 90% likelihood of a synucleinopathy[7] sufficient to justify a probable DLB diagnosis even in the absence of any other core feature or biomarker. RBD is characterized by loss of normal skeletal muscle atonia during REM sleep with prominent motor activity and dreaming[1,3,23,46,50]. RBD can occur without any coexisting neurological disorders or findings (so-called idiopathic RBD) and can be precipitated or aggravated by medications, such as selective serotonin or norepinephrine reuptake inhibitors[11,48]. All structural lesions associated with RBD identified to date have been localized in the dorsal midbrain, pons, or medulla.

□ SUPPORTIVE BIOMARKERS

- **EEG.** Resting-state electroencephalographic rhythms have extensively been used as a possible tool to assess the neurophysiological correlates of dementia[12,13,24]. Quantitative EEG has demonstrated good discriminative capacity for DLB diagnosis as compared to AD with a predictive value of 100% in cohort studies, even at the stage of MCI[9,10] and the percentage of 90% in a multicentric cohort study[8]. Specifically, discriminant analysis detected specific cut-offs for every EEG mathematical descriptor; dominant frequency = 8, dominant frequency variability = 2.2 Hz, frequency prevalence pre-alpha = 33%, FP alpha = 41% for posterior derivations. The occipital low frequency alpha 2 source activity showed a classification accuracy of 75% in the contrast between the AD and DLB patients[4].
- **STRUCTURAL IMAGING STUDIES (PRESERVATION OF MEDIAL TEMPORAL GREY MATTER).** Recent advance in structural MRI allows to perform physical measurements of brain cortical thickness for each individual and to map, within and between groups, the macrostructural changes in GM regions. The measurement of the cortical thickness[21] showed 82% sensitivity and 85% specificity in differentiating AD from DLB[28]. At cortical level, DLB patients show a preservation of medial temporal GM as compared to AD[14,17,38] and a thinning in the posterior areas including the precuneus, superior parietal gyrus, cuneus, pericalcarine and lingual gyri[17]. Of note, the posterior atrophy of the cuneus, precuneus and superior parietal cortex has been related to visual deficit and hallucinations in DLB[6,17]. Moreover, increased rates of cortical thinning in the parietal regions were also correlated with motor deterioration in DLB[33].
- **FURTHER EVIDENCES COMING FROM STRUCTURAL IMAGING STUDIES.** At subcortical level, microstructural and macrostructural alterations have been also described in DLB patients. Macrostructural assessment highlighted that the hippocampus, especially in the cornu ammonis and subiculum, is relatively preserved in DLB as compared to AD[16,33]. Grey matter (GM) reduction was also observed in DLB patients in the adjacent extrahippocampal structures including the perirhinal and parahippocampal cortices(16). Microstructural damage of GM subcortical nuclei in DLB patients has been observed in the pons, hippocampus and thalamus[18,19,32]. Additionally, by combining structural MRI and DTI data, the thalamus was further divided in sub-regions according to their structural connectivity to cortex. The assessment of microstructural changes in each thalamic sub-region in DLB have revealed: microstructural grey matter preservation of the sub-regions which projects to temporal cortex[19],

alterations within the thalamic portions projecting to the prefrontal and parieto-occipital cortices and amydala[19]. Moreover, DLB patients present reduced structural connectivity within the anterior thalamic radiation, which projects to frontal cortex[48]. These results are in agreement with the role of thalamus in shaping the cortico-cortical control[49] and with emerging hypotheses suggesting that thalamic dysregulation could induce reduced levels of arousal and consciousness state[2]. In this context, we observed reduction of NAA/tCr (marker of axonal density) and increase of tCho/tCr (marker of cholinergic dysfunction) in DLB patients, which correlated with frequency and severity of fluctuating cognition in DLB[18]. Moreover, it was observed that the microstructural damage of the thalamic portions projecting to cortical posterior regions including parietal and occipital lobes is closely related to the presence and severity of visual hallucinations[19]. These findings are in agreement with the role of the pulvinar in the visual processing[47] and with recent reports from neuropathological studies showing severe neuronal loss in the medial pulvinar in post-mortem brain tissue acquired from patients with DLB[20].

- **Cingulate island sign.** The CIS, a term referring to sparing of the posterior cingulate relative to the precuneus and cuneus, has been proposed as an FDG-PET imaging feature of DLB[27,31] due to its good diagnostic power to distinguish DLB patients from AD. The preservation of the CIS is not associated with Aβ load but does predict lower Braak neurofibrillary tangle stage in clinically diagnosed DLB cases[26]. Furthermore clinical symptoms of DLB (parkinsonism and global cognitive function) were found to be correlated with precuneus plus cuneus hypometabolism but not the CIS[26].

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Disclosure. *The Author declare no conflicts of interest.*

Review

Idiopathic normal pressure hydrocephalus: review of a curable disease

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SUMMARY: *Idiopathic normal pressure hydrocephalus is, generally, a communication hydrocephalus of intriguing pathophysiology, characterized by classical clinical triad described by Adams and Hakim, gait disturbance, dementia and urinary incontinence, in addition to ventricular dilation visible by brain imaging and normal cerebrospinal fluid pressure during lumbar punture. The disease, is defined as a clinicopathological condition related to the insufficient capacity to absorb cerebrospinal fluid, but the exact mechanism of the development of the clinical symptoms is not known. It is a chronic disorder affecting the elderly, reaching 0.2% in the age group of 70 to 79 years, and 5.9% for age 80 years and older. Idiopathic normal pressure hydrocephalus has been estimated to account for up to 10% of cases of dementia and is significant because it is treatable by ventriculoperitoneal shunting. Despite differences in disease etiology, several brain disorders in the elderly share dementia as a common clinical feature. The treatment for the majority of these disorders is merely symptomatic and does not modify the course of illness. Symptoms of idiopathic normal pressure hydrocephalus are the only ones that can be modified if they are recognized in time and treated appropriately. Clinicians play a paramount role in the identification of patients who should be evaluated for possible idiopathic normal pressure hydrocephalus and patients who can improve with shunt surgery. With contemporary diagnostic tests and treatment with adjustable valves, the benefit to risk ratio of shunt surgery is highly favourable. The introduction of programmable valves has dramatically lowered the need for shunt revisions and most complications can be handled by modifying the shunt setting.*

KEY WORDS: *Dementia, Elderly, Idiopathic normal pressure hydrocephalus.*

INTRODUCTION

Idiopathic normal pressure hydrocephalus is a syndrome generally found in elderly and is the most common form of hydrocephalus in adults. The disease, first described in 1965 by Hakim and Adams, is defined as a clinicopathological condition related to the insufficient capacity to absorb CSF, but the exact mechanism of the development of the clinical symptoms is not known(1). The prevalence of iNPH is age related, reaching 0.2% in the age group of 70 to 79 years, and 5,9% for age 80 years and older(13). Patients develop a syndrome characterized by communicating hydrocephalus with dilated cerebral ventricles, impaired gait, cognition and urinary control (urgency and incontinence). The CSF pressure checked at a diagnostic LP is normal.
Normal pressure hydrocephalus is usually described

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Progress in Neuroscience 2019; 4 (1-4): 33-40.
ISSN: 2240-5127
doi: 10.14588/PiN.2019.Ricciuti.33

LIST OF ACRONYMS AND ABBREVIATIONS: **AD** = Alzheimer Disease; **CDT** = Clock Drawing Test; **CSF** = CerebroSpinal Fluid; **CT** = Computerized Tomography; **DESH** = Disproportionately Enlarged Subarachnoid space Hydrocephalus; **ICP** = IntraCranial Pressure; **iNPH** = idiopathic Normal Pressure Hydrocephalus; **LP** = Lumbar Puncture; **MMSE** = Mini-Mental State Examination; **MRI** = Magnetic Resonance Imaging; **PD** = Parkinson Disease; **PM 47** = Progressive Matrices 47; **VP** = VentriculoPeritoneal shunt; **SVE** = Subcortical Vascular Encephalopathy; **TMT** = Trail Making Test.

as idiopathic, although it can be secondarily present in several disorders and conditions such as subarachnoid hemorrhage, infection, head trauma, cerebral tumors and in patients who have undergone an intracranial neurosurgical procedure.

The disease remains one of the most controversial neuropathological entities both in regards to its diagnosis and its proper clinical management. iNPH symptoms are not pathognomonic and may also be present in vascular dementia, AD, and PD, among many other less common diseases[14].

The only effective treatment for iNPH is CSF shunt, usually configured between the lateral ventricle and the peritoneum, the VP shunt[18].

The diagnosis of iNPH is based on a patient's clinical status, the natural history of the disease, imaging findings and clinical response to specific diagnostic procedure.

iNPH should be suspected in elderly patients presenting with unexplained, symmetric gait disturbance, which is the primary symptom of iNPH. Findings include difficulty with transitional movements, gait initiation failure, shuffling gait and poor foot clearance. Although dementia and incontinence are frequently present, the complete triad is not needed to suspect the disorder.

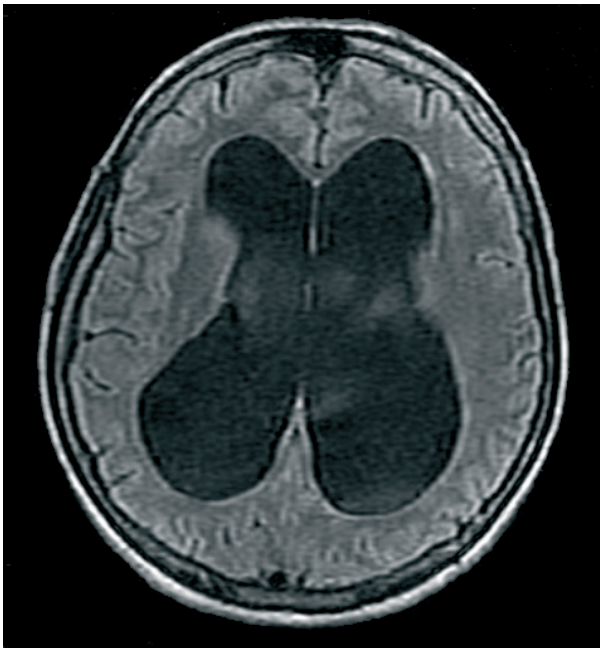

Figure 1. Evans' Index is the ratio of maximum width of the frontal horns of the lateral ventricles and the maximal internal diameter of the skull. Ratio is > 0.38.

Neuroimaging with either CT or MRI is required for the diagnosis of iNPH; however, MRI is preferable. CT scanning of the brain is useful if MRI is unavailable. MRI T2-weighted images are especially helpful.

As ventricular enlargement occurs with other dementias and to an extent with normal aging, a ratio of maximum width of the frontal horns of the lateral ventricles and the maximal internal diameter of the skull, known as the Evans index, of > 0.3 has been proposed to correlate with iNPH(28) (Figure 1).

A further important role of neuroimaging is to asses for hydrocephalus with ventriculosulcal disproportion that is a disproportionate widening of the ventricles in comparison to the cerebral sulci. Japanese researchers have described this as DESH[9,12,13]. A coronal section at the level of the posterior commissure reveals a narrow subarachnoid space surrounding the outer surface of the brain (a "tigh convexity) and narrow medial cisterns (Figure 2).

Clinical presentation and neuroimaging abnormalities suspecting for iNPH are usually not sufficient to recommend shunt surgery. Predictive tests to determine the likelihood of surgery responsiveness are suggested. Subtraction tests used to raise the prognostic accuracy are the spinal tap test and the continuous spinal drainage. Infusion testing for assessment of CSF hydrodynamics is commonly used in Europe to diagnose iNPH and rarely in Canada and United States.

The spinal tap test consists with the removal of 30 to 70 mL of CSF with lumbar puncture. The CSF subtraction can be repeated for two or three consecutive days. The continuous spinal drainage of 150 to 200 mL of CSF per day for 2 to 7 days is conducted with an external lumbar drainage.

These tests are considered to be positive if the number of steps taken in a 10 meters gait test, and the time needed to walk 10 meters, are reduced by at least 20% and psychometric tests show an improvement of

at least 10%. The CSF infusion test involves infusing Ringer lactate via one spinal needle while simultaneously recording CFS pressure via a second spinal needle. Several methods for infusion testing exist but one of the most consistent findings in iNPH research is that the patients have an increased resistance to CSF outflow (Rout)[15,23].

Finally long-term recording of ICP for 24 to 72 hours has been used as a diagnostic test for iNPH for 40 years. Such techniques are not recommended for routine use currently. Elderly patients with obstructive hydrocephalus may present with symptoms of iNPH. In such cases diagnostic ICP measurement via intracranial methods should be considered to submit patients to third endoscopic ventriculostomy (Figure 3 and 4).

Aims. The purpose of the Authors was to define the iNPH as clinical entity and to suggest a diagnostic and therapeutic method to manage it, evaluating the actual context of scientific literature and own experience based on a multidisciplinary collaboration.

☐ MATERIALS AND METHODS

This article is based on a selective review of literature, including current guidelines, carefully selected review article published in English since 2001, and original article retrived by a PubMed search.

☐ DISCUSSION AND CONCLUSION

According to Hakim and Adam's hypothesis, iNPH occurs when CSF absorption is decreased resulting in increased chronic intracranial pressure. Over time, ventricular enlargement occurs as a compensatory

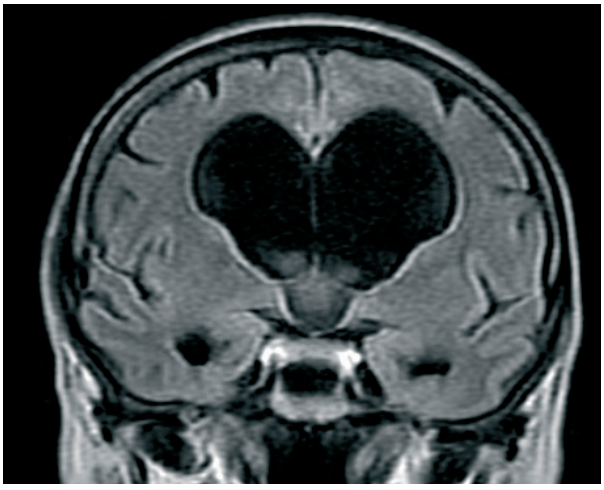

Figure 2. Coronal section at the level of the posterior commissure reveals a narrow subarachnoid space surrounding the outer surface of the brain (a "tight convexity") and narrow medial cisterns.

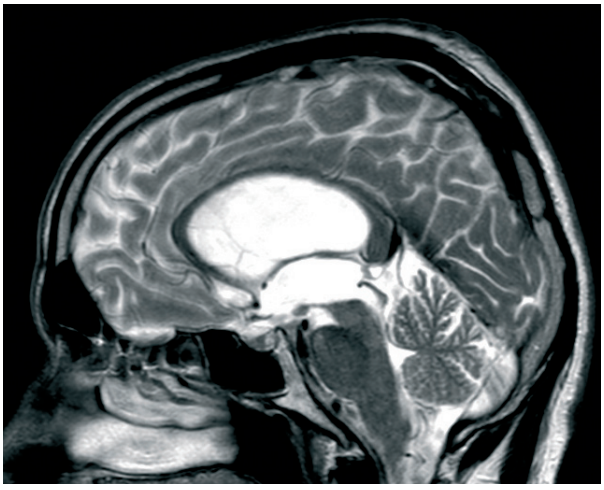

Figure 3. Sagittal T2 MRI shows obstructive hydrocephalus.

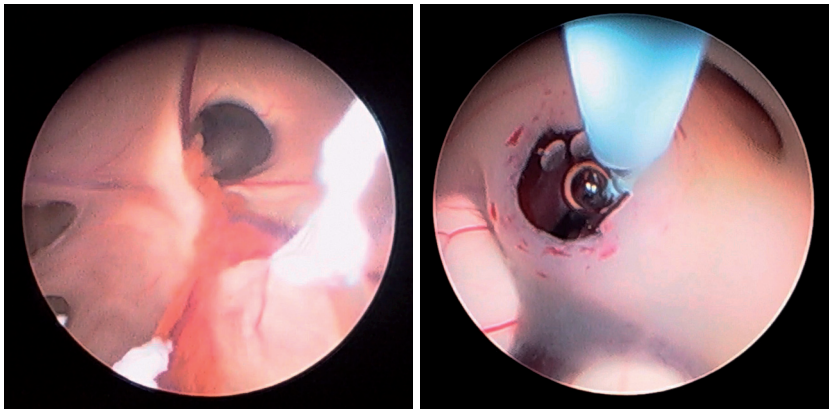

Figure 4. Endoscopic third ventriculostomy phases.

Characteristics	Clinical Findings
Step frequency in gait test (10 m)	Number of steps > of 13; duration > 10 "
Step breadth	Distance between toes > 1 foot lentgh
Step lenght	Distance < 1 foot lenght
Turn on yourself	> 4 to 6 steps
Bipedal gait	Correction of foot position > 25% of steps

Table 1. Features of gait impairment in iNPH.

mechanism. This results in a new intracranial pressure steady state. As a modification, CSF flow is directed more toward the Virchow-Robin spaces into brain parenchyma1. Parenchymal changes occur resulting in tissue compression and deep white matter ischemia, hallmarked by myelin pallor.

Idiopathic normal-pressure hydrocephalus is characterized by a combination of clinical and radiological findings arising in adulthood. The cardinal symptoms of iNPH are gait impairment, dementia, and urinary incontinence. Imaging studies of the brain reveal ventriculomegaly without any marked degree of cortical atrophy.

However, these symptoms are not pathognomonic and may also be present in vascular dementia, AD, PD, among many other less common diseases[14].

Impairments of gait and balance are typically the first symptoms to be noticed and may be very mild at the outset. They are also the most likely to improve after CSF shunting, with a probability of more than 85%[11]. Patients may initially complain of dizziness, difficulty walking on a slope or stairs, and difficulty getting up from or sitting down on a chair. As the disease progresses, the patient's gait deteriorates markedly, becoming broad-based, slow, short-stepped, and glue-footed (a gait disturbance of the abasia-astasia type). Table 1 describe characteristics of gait impairment in iNPH.

Some patients with iNPH present with mild cognitive impairment rather than dementia. The major cognitive impairments in patients with iNPH are frontal lobe symptoms, such as psychomotor slowing and impairment of attention, working memory, verbal fluency and executive function. The cognitive and behavioral disturbances accompanying iNPH have been commonly described as "fronto-subcortical dementia"[19,26]. iNPH patients failed on attentional tasks which may reflect a deficit in cognitive flexibility, similar to patients with frontal lobe excision and patients with fronto-subcortical dementia such as Parkinson's disease[20,21], and unlike patients with Alzheimer Disease in which frontal functions are spared[22].

To assess the cognitive impairments in iNHP numerous neuropsychological assessment were used, investigating different cognitive domains to evaluate the effects of CSF shunt surgery on cognitive dysfunction[8,24].

The MMSE is widely used to screen for cognitive impairment in adults providing a global score of cognitive ability.

Abstract reasoning was assessed by "Raven's coloured progressive matrices PM 47"[6]. PM 47 are a multiple choice intelligence tests and in each test item, the subject is asked to identify the missing item that completes a pattern.

To assess focused and divided attention visual search tasks were used. These tests were used to assess the ability to detect a target element embedded in a series of distractor elements. It predicts both response time and error rates. Visual Search Task[25] is an attention test that requires some selectivity, as all stimuli are irrilevant except the ones designated as target. In TMT[10], all numbered circles are to be regarded as "noise" except the number that the subject is searching for. The Stroop Color-Word Test[4] was used to assess the selective attention and the sensitivity to interference.

Digit span forward/backward[17] was used to assess verbal short-term memory and verbal working-memory. Sequences of digits increasing in number are orally presented and the subject has to either repeat it in the original (forward) or the reversed order (backward). Spatial span backward/forward was used to assess visuospatial short-term memory and visuospatial working-memory. To evaluate visuoconstructional abilities the CDT[5] were administered. This test required participants to draw the contour, numbers, hands, and center of the clock. In the prose memory test[25] the patient is asked to

Disease	Atypical INPH features	Common features with iNPH
Cortical Dementia		
Alzheimer's disease	Focal cortical deficits; appearance of gait problems when dementia is severe	Dementia without gait impairment is very rare
Fronto-Temporal dementia	Personality change, psychiatric abnormalities; disinibition, impulsiveness, irritability, emotional lability, aphasia, no motor disturbance, incontinence is very rare	
Subcortical Dementia		
Lewy-Body Dementia	Visual hallucinations, delusions, markedly fluctuating cognitive function	Gait impairment and dementia
Parkinson's disease and vascular parkinsonism	Rest tremor, unilateral onset; speed of movement can be increased with the aid of external stimuli (this is not the case in NPH). The patient cannot simulate walking and bicycle-riding while supine; no broad-based gait with externally rotated feet; mildly reduced step height, markedly reduced arm swing, markedly stooped posture, autonomic dysfunction	Hypokinetic gait, tremor (40%) in iNPH
Progressive supranuclear palsy	Pseudobulbar palsy, supranuclear upward gaze paresis	Frontal brain signs, impaired executive function, gait disturbance
Corticobasal degeneration	Rigor, asymmetrical symptoms, alienlimb phenomenon, apraxia, supranuclear upward gaze paresis, cortical sensory deficits, severe loss of postural control	
AIDS-dementia complex	Positive HIV serology	Psychomotor slowing, impairment of memory and concentration, gait impairment due to HIV myelopathy
Age-related depressione	Depressive thought content because of frequently comorbid vascular dementia, sometimes other features as well	Pseudodementia, neuropsychological test findings very similar to those seen in NPH
Mixed Dementia		
Vascular Dementia	Asymmetrical (sometimes transient) symptoms, possibly correlated with lesions seen in imaging studies	Thought disorder, impaired executive function

Table 2. Dementia differential diagnostic criteria.

recall a short passage of prose read by the examiner. The verbal fluency test was used to evaluate executive functions and the ability to generate words fluently in a phonemic format (Phonemic Fluency Test)[6] or from overlearned concepts (Semantic Fluency Test)[7].

Several studies report that patients with iNPH are impaired in various aspects of cognition involving both 'frontal' executive functions and 'posterior cortical' functions and report that after shunt operation, cognitive impairment improves but marked improvement in cognitive functions is less frequent than that of the gait disorder. Table 2 described the main features for differential diagnosis between dementias.

Urinary urgency and frequency are the most common urinary symptoms and may occur with or without incontinence. Patients are usually aware of the urinary urge and are concerned about their incontinence. Because bladder symptoms are very common among elderly, other causes are frequently present in patients with suspected iNPH.

The presence of commorbidities doesn't exclude the possibility of iNPH. However commorbidities do influence the prognosis after shunt surgery.

Distinguishing dilated ventricles due to cerebral

atrophy from iNPH is sometimes difficult. Typical findings of iNPH include disproportionate widening of the ventricles in comparison to the cerebral sulci. Changes in the signal characteristics of periventricular tissue must be interpreted with caution. SVE may cause changes quite similar to those seen in iNPH as a result of transependymal CSF diapedesis. Periventricular white matter lesions immediately adjacent to the ventricular wall are considered to reflect fluid movement from ventricles into the parenchyma, but white matter lesions that are more peripheral or more diffuse and confluent are more likely to represent ischemic changes.

Moreover, Evans' index detected on neuroimaging is only a rough marker for ventriculomegaly, and thus, there has been recent debate of its accuracy and reliability in iNPH diagnosis[27]. A recent new Evans index is proposed by M.K. Beyer et al.[3] resulting that it cannot be applied to separate healthy elderly controls from patients with AD due to low sensitivity, but may separate separate healthy elderly controls from iNPH patients with high sensitivity. When applying the proposed cut-offs for Evans index in men and women aged 65-84 years (0.34-0.37), they differantiated between iNPH and CTR with a sensitivity of 80%. In iNPH, the Sylvian fissures are often widened out of proportion to the cortical sulci, which are flattened. This feature could suggest a block of CSF flow over the cerebral convexity to the arachnoid granulations.

The international guidelines recommend tests of CSF hydrodynamics (tap test, external lumbar drainage and infusion testing) to demonstrate either that the patient has the potential to respond to shunt surgery or that the patient has abnormal CSF hydrodynamics that are consistent with hydrocephalus[2,11,18,23].

External lumbar drainage involves continuous CSF drainage and requires hospitalization. This procedure is said to be accurate, with both a high positive-predictive value and a high negative-predictive value. The most frequent serious complication of external lumbar drainage is bacterial meningitis, seen in 2% to 3% of patients. Because the possibilities of this complication and the need for hospitalization, in our unit we prefear to use tap test to check the possibility for surgery.

The tap test, also known as the large volume LP, should be done with an 18 or 20 gauge spinal needle, usually removing 30 ml to 50 ml of CSF. The interval between the LP and the formal follow up examination is usually between 3 and 6 hours with 10-meters gait test and neuropsychological exams. The patient does not have to stay supine after the LP, and usually headache and nausea after LP are uncommon in the iNPH population. The CSF subtraction can be repeated for two or three consecutive days.

The absence of response to CSF removal does not exclude shunt responsiveness because the tap test is specific (range of 50% to 100% in various studies), rather than sensitive (range of 50% to 80%).

We perform lumbar infusion test when tap test is not significant in the patients with high iNPH still clinical suspect. Kahlon et al. have found the false negative predictions in the operated patients are much higher (58%) with the tap test than with lumbar infusion test (16%)[15,16].

Shunt surgery is treatment of the most cases of iNPH, in only few iNPH patients third endoscopic ventriculostomia is appropriate. The purpose of shunt is to divert CSF from craniospinal CSF space to another anatomic space were CSF can be reabsorbed. The most common configuration is VP shunt.

Two types of shunt valves are widely used: shunt with a fixed-valve opening pressure and programmable shunts with variable valve opening pressure that can be changed via an external magnetic programming device. No evidence supports the use of one specific make or model of shunt over another. We prefear use programmable shunts with variable valve opening pressure to manage eventualy shunt's serious complication, such as subdural effusion or hematoma. Adjustable valves offer the advantage of being able to lower the pressure setting incrementally until symptoms improve and to raise the pressure setting if flow-pressure symptoms or complications emerge.

The introduction of programmable valves has dramatically lowered the need for shunt revisions and most complications can be handled by modifing the shunt setting[29].

In meantime, however, improved diagnostic and therapeutic methods, have raised clinical successful into the range of 70% to 90%, and the risk benefits analyses have shown beyond any doubt that surgery for iNPH is far better than conservative treatment or the natural course.

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Disclosure. *The Author declare no conflicts of interest.*

Review

Molecular imaging in neurodegenerative forms of dementia

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SUMMARY: *Cognitive dysfunction and dementia are a common consequence of several types of neurodegenerative disorders. Yet, there are numerous challenges in the differential diagnosis of neurodegenerative forms of dementia, which have hampered the successful implementation of clinical trials and development of new disease-modifying therapies. One of the main issues is represented by patients' heterogeneity at different levels, from the molecular and pathological aspects, to the presentation of overlapping and often mixed clinical phenotypes and syndromes. Different molecular brain imaging techniques such as PET or SPECT represent important diagnostic tools for investigating and tracking the brain pathological changes in neurodegenerative disorders leading to dementia. Molecular imaging also promises to revolutionize our understanding of the complex and often shared pathological pathways underlying different neurodegenerative forms of dementia and to disentangle the clinical phenotypes via neurobiologically meaningful biomarkers. I review the most important, significant, and up-to-date results from molecular imaging research (PET and SPECT studies) in neurodegenerative forms of dementia including amnestic Alzheimer's disease, its prodromal stage of mild cognitive impairment, atypical forms of Alzheimer's disease, frontotemporal lobar degeneration syndromes, Parkinson disease with cognitive impairment, and dementia with Lewy bodies. Overall, past and more recent research has clearly demonstrated the value of using molecular imaging techniques to guide the differential diagnosis in neurodegenerative forms of dementia. Future studies should assess the potential utility of molecular imaging to empower clinical trials via unravelling the patient-specific pathological and clinical heterogeneity.*

KEY WORDS: *Alzheimer's disease, Frontotemporal dementia, Parkinson's disease, PET, Neurodegeneration, SPECT.*

INTRODUCTION

Dementia can be caused by several different forms of neurodegenerative conditions which cause irreversible and progressive dying of the neurons in the central nervous system[4,49,59]. These syndromes usually affect elderly people, although in some cases (e.g., genetic forms) young adults can suffer from devastating forms of dementia driven by neurodegenerative disorders[8]. Although classified as distinct diseases, the clinical presentation and underlying molecular etio-pathogenesis can overlap in apparently different disorders including Alzheimer's disease, frontotemporal dementia, and Parkinson's disease[5]. The complexity of the clinical spectrum in these diseases and the multifaceted nature of the underlying pathology makes sometimes the differential diagnosis amongst these neurodegenerative disorders difficult[7].

Novel and established molecular imaging techniques have thus the potential to guide the clinical diagnosis

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Progress in Neuroscience 2019; 4 (1-4): 41-52. *ISSN: 2240-5127*
doi: 10.14588/PiN.2019.Passamonti.41

LIST OF ACRONYMS AND ABBREVIATIONS: **3R/4R** = 3 repeat/4 repeat (tau); **1C-PiB** = 11C-labeled Pittsburgh compound-B; **AD** = Alzheiemer's Disease; **ALS** = Amyotrophic Lateral Sclerosis; **APP** = Amyloid Precursor Protein; **bvFTD** = behavioural variant of the FrontoTemporal Dementia; **CBD** = Cortico-Basal Degeneration; **CBS** = Cortico-Basal Syndrome; **DAT** = Dopamine transporter; **DLB** = Dementia with Lewy Bodies; **FDG** = Fluoro-Dexosi-Glucose; **FTLD** = FrontoTemporal Lobar Degeneration; **lvPPA** = logopenic variant of primary progressive aphasia; **MCI** = Mild Cognitive Impairment; **MRI** = Magnetic Resonance Imaging; **PCA** = Posterior Cortical Atrophy; **PD** = Parkinson Disease; **PDD** = Parkinson Disease Dementia; **PET** = Positron Emission Tomography; **PNFA** = Progressive Non-Fluent Aphasia; **PPA** = Primary Progressive Aphasia; **PS1** = PreSenilin 1; **PS2** = PreSenilin 2; **PSP** = Progressive Supranuclear Palsy; **SPECT** = Single Photon Emission Computed Tomography; **TDP-43** = TAR DNA-binding protein 43.

and in some circumstances can offer new insights into the etio-pathogenesis of these conditions[36,63]. A promising and emerging application of molecular imaging is also that of providing reliable biomarkers that can be employed to stratify patients in clinical trial to provide objective assessment tools to track the disease evolution and the potential utility of new treatments, even before an effect detectable at the clinical level[36,63]. Patient heterogeneity in molecular, pathological, and clinical terms is usually high and it is one of the main drivers of null results in clinical trials. Stratifying single patients via the use of neuro-imaging techniques that characterize the degree of their pathological complexity and heterogeneity holds the promise of empowering clinical trials that aim at halting or reverting the devastating effects of neurodegenerative disorders.

☐ ALZHEIMER'S DISEASE AND MILD COGNITIVE IMPAIRMENT

❐ Typical forms of Alzheimer's disease

Alzheimer's disease and its prodromal stage of mild cognitive impairment are the most common neuro-degenerative forms of dementia, which affect around 53 millions of people around the world in 2018. It has also been estimated that every 65 seconds someone in the USA develops Alzheimer's disease[2].

The typical age of onset of AD is around 65-70 years and the most commonly reported symptoms in the typical form of AD are represented by episodic memory deficits[22]. In less typical forms of AD language and semantic impairment, as well as prominent problem in executive functions have been reported[22]. Although the current criteria for the diagnosis of AD are inherently clinical in nature[49], there are continuous attempts to develop reliable diagnostic tools for an early diagnosis of AD. This is particularly true for the complex clinical spectrum of MCI which in some cases (around 10-15%) covert into AD in around 4.5 years[43].

The AD's spectrum of disorders has two molecular hallmarks that can be assessed via advanced molecular imaging techniques: the amyloid burden and the presence of the abnormal accumulation of the tau protein[66]. Hyper-phosphorylated tau contributes to form the characteristic neurofibrillary tangles observed *post mortem* in AD[66]. The causal links between amyloid deposition, abnormal tau accumulation, and neurodegeneration are not fully resolved, although the progression of the neuronal dying follows a specific pattern that is described in the Braak staging system[11]. In early forms of AD, the cellular loss is localized to the medial temporal regions including the amygdala, hippocampus, entorhinal, and para-hippocampal cortex[11]. This neurodegenerative pattern also explains the early presence of episodic memory impairments. More recent studies have extended the early stages of AD to include other sub-cortical regions and brainstem areas such as the basal forebrain nuclei and the locus coeruleus, in which early signs of AD-related pathological changes can be detected even before damage to the medial temporal lobe system[3].

The next stage in the pathological and clinical progression of AD is represented by the involvement of the neocortex, in particular the posterior regions such as the temporo-parietal cortex[11]. The primary sensory/motor regions such as the visual cortex remain relatively spared from the AD-related neuro-degenerative processes even at relatively late stages of the disease[66]. One of the main challenges of the molecular imaging in AD and related disorders is to tackle its molecular and clinical heterogeneity to provide reliable measures that quantify the degree of amyloid and tau pathology. These measures could be used to personalize new disease-modifying treatment that target the amyloid and/or tau burden.

❐ Atypical forms of Alzheimer's disease

A relatively small proportion (around 5%) of patients with AD display an early-onset of the disease (before 65 years of age)[8]. In these cases, genetic mutations in

the APP, presenilin (PS1 or PS2) gene can be detected[8]. The clinical spectrum of these inherited conditions can vary, although they tend to share the classic AD pathological features at the post-mortem level (amyloid plaques, neurofibrillary tangles)[22].
Another form of atypical AD is represented by the PCA[14]. Although the post-mortem characteristics of PCA highly resemble those of AD pathology, at the phenotypic and clinical level the predominant syndrome is characterized by severe deficits in visuo-spatial skills, difficulty in orientation, and constructional apraxia[14].
The logopenic variant (or logopenic aphasia) is part of the PPA spectrum of diseases which spans clinical and pathological features with the frontotemporal lobar degeneration syndromes as well as AD[28]. The main clinical features of AD-related forms of logopenic aphasia are the presence of impaired word retrieval and sentence repetition in the absence of motor speech abnormalities or agrammatism[28].
AD-related pathology can also lead to parkinsonian disorders such as the CBS, a complex and pathologically heterogeneous condition which can be caused by AD or frontotemporal related pathology[27]. At the clinical level, patients with CBS often display a parkinsonian syndrome which is associated with cortical deficits including apraxia, speech disorders (agrammatism, progressive non-fluent aphasia), alien limb features, and sensory cortical loss (astereognosis and agraphesthesia)[27]. The CBS cases with underlying AD pathology are not distinguishable from those affected by FTD-related pathological changes[27]. This is thus a condition in which the molecular imaging plays a fundamental role for the differential diagnosis of the underlying pathological causes of this neurodegenerative disorder.

☐ MOLECULAR IMAGING IN ALZHEIMER'S DISEASE AND RELATED DISORDERS

❒ Fluoro-Dexosi-Glucose positron emission tomography

In the past, one of the most widely used molecular imaging techniques to assess patients with AD-related disorders has been represented by the FDG PET imaging. FDG PET assesses the degree of regional glucose metabolism and consequently is an indirect measure of perfusion, brain atrophy, and function. FDG PET studies in AD have consistently demonstrated abnormal decrease in the glucose metabolism in posterior regions including temporo-parietal cortices, posterior cingulate cortex, and medial temporal lobe regions such as the amygdala and hippocampus[12,37,50]. Longitudinal studies using FDG PET have also found that AD progression is related to decline in glucose metabolism in posterior cortical regions, consistently with the clinical syndrome of AD[1,67]. FDG PET imaging has also been valuable in demonstrating significant changes in metabolism in elderly individuals at risk to develop AD due to genetic factors or the presence of mild cognitive impairment[67]. The main limitation of the use of FDG PET in assessing AD-pathology is constituted by its inability to distinguish the effect of regional atrophy or vascular changes over and above the metabolic effects. FDG PET is also not suited to quantify the underlying molecular pathology of AD, namely amyloid deposition and tau burden.

❒ Amyloid PET tracer

The ^{11}CPiB PET tracer has revolutionized the molecular imaging of AD and has allowed to track for the first time *in vivo* a critical pathological aspect of AD[30,35]. As expected from post-mortem research, patients with AD and some forms of MCI which are likely to convert to AD, display increased binding of the ^{11}CPiB PET tracer in several brain regions including the frontal, temporal, and parietal lobes[20]. The ability of the ^{11}CPiB PET tracer to identify AD pathology is elevated and around 96% of the AD patients are found to display positive ^{11}CPiB PET scan[33]. Even more importantly, longitudinal studies using ^{11}CPiB PET have revealed that MCI patients with positive ^{11}CPiB PET scan are more likely to convert to AD[16]. Likewise, individuals at high risk of developing AD due to genetic mutations show increased amyloid burden with ^{11}CPiB PET[61]. However, the ^{11}CPiB PET has shown limited ability to characterize the phenotypic complexity in AD[54]. In other words, there is poor correlation between the ^{11}CPiB PET signal and the clinical disorder of AD, in terms of localization of the clinical syndromes and in terms of regional deficits in glucose metabolism[54]. In other words, the amyloid burden that is quantified by the ^{11}CPiB PET tracer can be diffused or scattered to several regions of the brain, even those which might not have immediate clinical relevance at the

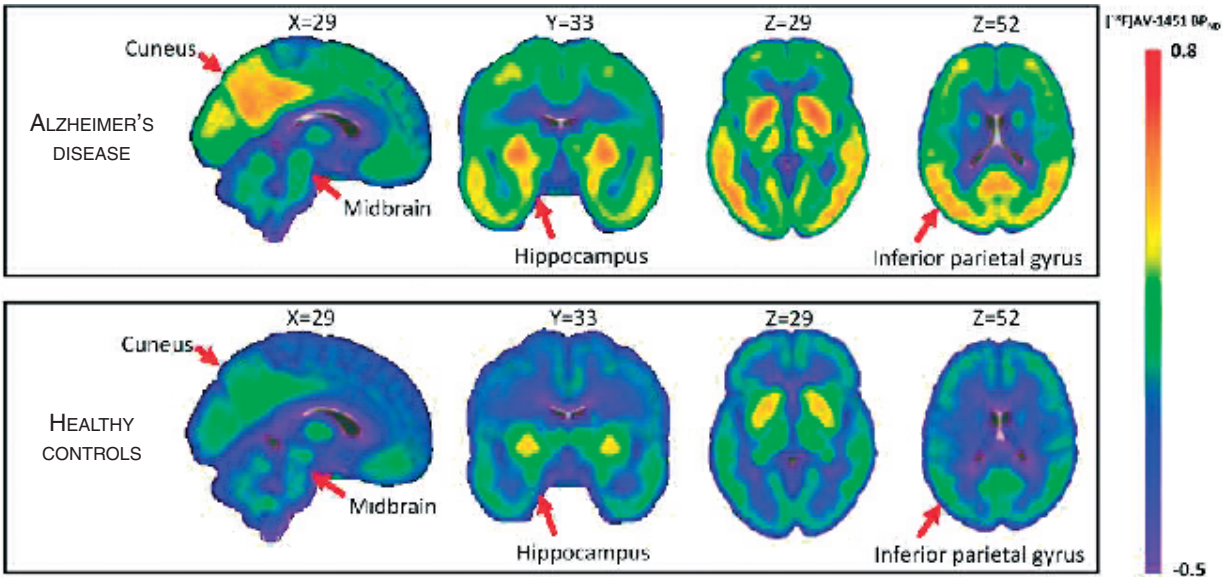

Figure 1. Mean [^{18}F]AV-1451 positron emission tomography map in each group. Note the overall high [^{18}F]AV-1451 binding in the basal ganglia in both groups including controls. Patients with Alzheimer's disease pathology showed increased [^{18}F]AV-1451 binding in the medial temporal lobe regions and other cortical areas, relative to controls[65].

symptomatologic and clinical level[54]. The correlation between the amyloid burden detected via ^{11}CPiB PET tracer and glucose hypometabolism, brain atrophy, and disease progression is also modest[54].

❒ Tau PET tracers

More recently, new and promising compounds, which bind to the tau protein, have been developed. These include ^{11}C-PBB3; ^{18}F-AV-1451 (or "flortaucipir", previously known as T807), and the "THK" group including ^{18}F-THK523, ^{18}F-THK5105, and ^{18}F-THK535[47]. All these ligands have shown a good ability to tack the pathological accumulation of the tau protein in AD and have been able to detect the typical AD evolution described in the Braak staging system[71] (Figure 1). The advent of tau imaging in AD therefore represents an important milestone for the development of new disease-modifying clinical trials that aim at targeting the tau protein[71]. The novel tau tracers show good clinico-pathological correlations and are able to discriminate amongst the less typical form of AD syndromes including PCA, logopenic variant of AD, and CBS[72]. There is also evidence that tau PET tracers are able to reveal the age-dependant accumulation of tau seen in elderly individuals and in monitoring the various stages of deposition of the tau described by Braak and Braak[46,65]. Nevertheless, there are limitations of these new PET tau tracer which are almost related to their 'off-target' binding properties[38]. Another issue regards the specificity of these tau tracers to different iso-forms of the tau protein[52]. This is an important issue as AD and non-AD dementia (e.g., FTLD syndromes) are characterized by different iso-forms of tau, namely the 3R and 4R[17]. More specifically AD-related tau accumulation is characterized by a 3R/4R mixture, while in FTLD syndromes, one isoform is usually prevalent over other ones[17]. The chemical complexity of the tau isoforms thus represents a challenge to characterize the tau burden in neurodegenerative disorders. Off-target binding to neuromelanin or iron-related components such as micro-haemorrhagic lesions in the striatum or the choroid plexus have also been reported for some of the tau tracer[38]. A better understanding and characterization of the possible unspecific pattern of binding of these newly developed tau tracers is thus urgently warranted before these novel tools can be fully implemented in the clinical practice.

☐ FRONTOTEMPORAL LOBAR DEGENERATION

❒ Clinical spectrum of FTLD syndromes

The FTLD spectrum of disorders is an overarching

neurodegenerative condition that includes clinically heterogeneous diseases such as the PSP, CBD, PPA, and the bvFTD[13,28]. The clinical phenotypes of these conditions can be very variable although some behavioural features such as apathy, impulsivity, behavioural dys-inhibition tend to be present to a certain extend in all of these conditions, while the language disorders or the severe parkinsonism and balance problems tend to be more evident in the PPA and PSP, respectively[13,28]. As discussed before, around 1/3 of the cases with CBS display AD-related pathology while the remaining part are caused by FTLD-related pathology[27]. At the molecular level, the FTLD disorders is highly heterogenous and in many cases the pathology overlaps across the clinical spectrum[41].

The bvFTD is most often caused by tau pathology such as that observed in Pick's disease, although abnormal accumulation of the TDP-43 can also be a feature[41]. Patients with bvFTD have highly significant behavioural problems including severe personality changes, abnormal appetite, and obsessive compulsive symptoms[58,68].

Some cases of with bvFTD also display motor neuron diseases resembling ALS[6]. At the post-mortem level, TDP-43 pathology is present while genetically there is an high rate of mutation in the C09orf72 gene, which is hypothesized to play a key role in intra-cellular membrane traffic including exocytosis and endocytosis[32].

The PPA syndrome is divided in three forms (i.e., semantic dementia, PNFA, and logopenic aphasia), two of which are caused by FTLD-related pathology (semantic dementia and PNFA) and one of which by AD-related pathology (logopenic aphasia)[24]. At the clinical level the semantic form of PPA is characterized by anomia, deficits in single words comprehension, and only later in the course of the disease by behavioural features similar to those described in the bvFTD[24]. Of note, the majority of the cases of patients with semantic dementia show pathological accumulation of the TDP-43 protein, although rare cases witch Pick's related tau pathology have been reported[29].

PNFA's clinical picture is characterized by non-fluent aphasia, apraxia of speech, and agrammatism with no problems in sentence repetition or understanding[24]. Pathologically, PNFA can be caused by tau or TDP-43 pathology[25].

❒ Molecular imaging in FTLD syndromes

■ **FDG and amyloid PET tracer.** Given the molecular, pathological, and clinical complexity of FTLD syndromes there are at the moment limited molecular imaging studies and consequently few assessment tools to tackle the heterogeneity of the pathologies underlying FTLD syndromes. Despite these limitations, FDG PET studies have consistently found that the glucose metabolism is significantly reduced in patients with FTLD syndromes especially in fronto-temporal cortices[21]. More specifically, patients with logopenic aphasia due to AD have been reported to show reduced FDG metabolism in the left temporo-parietal areas[42] (Figure 2). A high rate of positivity at the amyloid PET in these patients also confirmed *in vivo* the underlying AD-related pathology[48]. On the opposite side, patients with the bvFTD variant have been found to have reduced FDG metabolism in the prefrontal cortex, consistently with their clinical syndrome of disinhibition and behavioural dysregulation[15].

FDG PET is also able to identify the functional neuroanatomy in semantic dementia by showing reduced glucose metabolism in the left anterior temporal pole, a key 'hub' region involved in semantic knowledge[34]. Furthermore, patients with semantic dementia typically show negative amyloid PET scan, which is consistent with their underlying pathology (TDP-43 accumulation)[70]. Likewise, patients with progressive non-fluent aphasia show reduced FDG metabolism in the left anterior insula[51]. In some of the cases of patients with PNFA (10%), amyloid positivity has been detected which emphasizes the molecular complexity of the FTLD clinical phenotype[64]. For those cases of patients with FTD and motor neuron disease, FDG PET is able to reveal hypometabolic patterns that encompass the frontal and temporal lobes[31].

To summarize, FDG PET in FTLD syndromes is capable of characterizing the clinical spectrum of FTLD, although, similarly to AD-related disorders, FDG PET is not able to discriminate between regional atrophy and metabolic effects, which remains the main limitation of this technique. Discriminating AD from FTLD could also be challenging with FDG PET especially in those cases in which the clinical symptoms overlap. In this context, the ^{11}CPiB PET tracer can

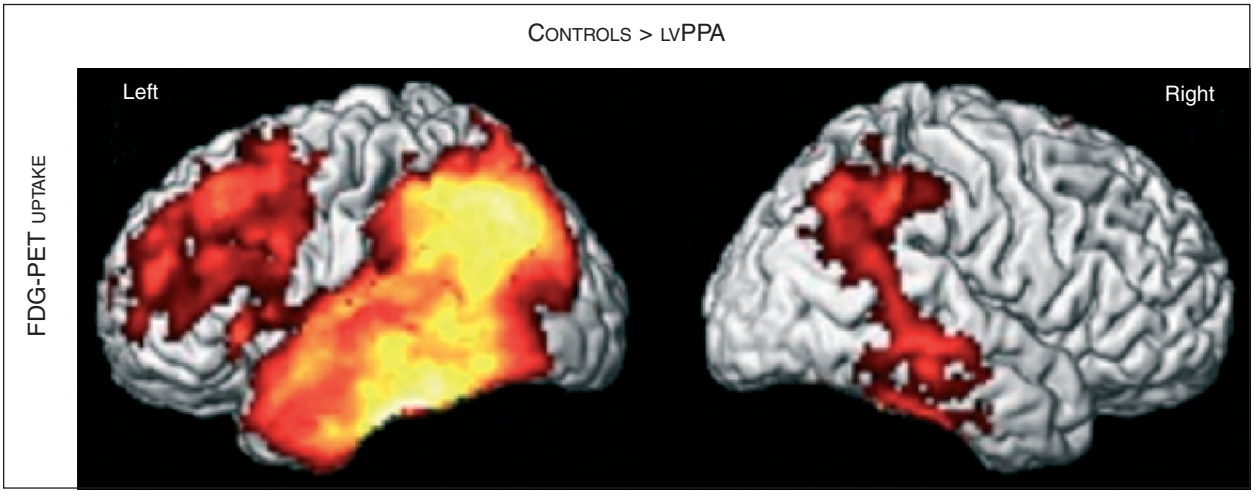

Figure 2. Patients with the logopenic variant of primary progressive aphasia due to Alzheimer's disease pathology show reduced FDG-PET binding (reflecting decreased glucose metabolism) in temporo-parietal regions, especially in the left hemisphere[42]. Legenda: L = left; R = right;

play an important role. Even in some tertiary centres, there is still a rate ranging between 10% to 40% of misdiagnosis between AD and FTLD syndromes but new techniques combing FDG PET and MRI have shown that it is possible to achieve an accuracy of up to 92% in the differential diagnosis between FTLD syndromes and AD[15] (Figure 3). The use of ^{11}CPiB PET tracer can help differentiating between AD and FTLD, although some studies have reported a low rate (9-10%) of PiB positivity in small series of FTLD cases, depending on the clinical phenotype[64]. In any case, a recent study in n = 62 AD patients and n = 45 FTLD cases showed that the sensitivity of PiB in discriminating between the diagnoses was higher than FDG PET (89.5% *vs* 77.5%), although both techniques showed comparable specificity (83% *vs* 84%)[60].

- **TAU TRACERS.** There is accumulating evidence that tau tracers such as C-PPP3 bind to tau inclusion in post-mortem tissue from patients with PSP or CBD. However, there are also data showing that another commonly used tau tracer such as AV-1451 display significant 'off-target' binding to neuromelanin, and iron-related components which have not been fully resolved[38]. *Post-mortem* studies also found that although AV-1451 specifically binds to AD-related tau pathology, there is little binding of the same tracer to non-AD tau pathology as that observed in FTLD syndromes[44]. Other recent study confirmed the strong AD-related binding of the AV-1451 PET ligand and reported only moderate binding of the same compound to pathological tissue from patients with FTLD syndromes including CBD and PSP[45]. Nonetheless, my recent research was able to demonstrate that AV-1451 PET is able to discriminate between two clinically very different types of tauopathies, namely AD and PSP[17]. There is also evidence that AV-1451 PET binding recapitulates the pathological hallmarks seen in FTLD syndromes and in genetic carriers of mutations linked to FTLD syndromes[9-10]. Hence, despite the off-target binding the regional specificity offered by the AV-1451 PET tau imaging might still provide valuable information to help the differential diagnosis between AD-related and FTLD syndromes over and above the presence of off-target binding[17].

☐ PARKINSON'S DISEASE WITH DEMENTIA AND DEMENTIA WITH LEWY BODIES

❒ CLINICAL SPECTRUM OF PDD AND DLNB

Parkinson's disease with dementia and dementia with Lewy bodies are two linked parkinsonian syndromes caused by the abnormal accumulation of the alfa-synuclein protein which can be identified in the Lewy-bodies, the characteristic pathological hallmark of PD and DLB[69]. The boundaries between PDD and DLB are not well defined, although at the clinical level the

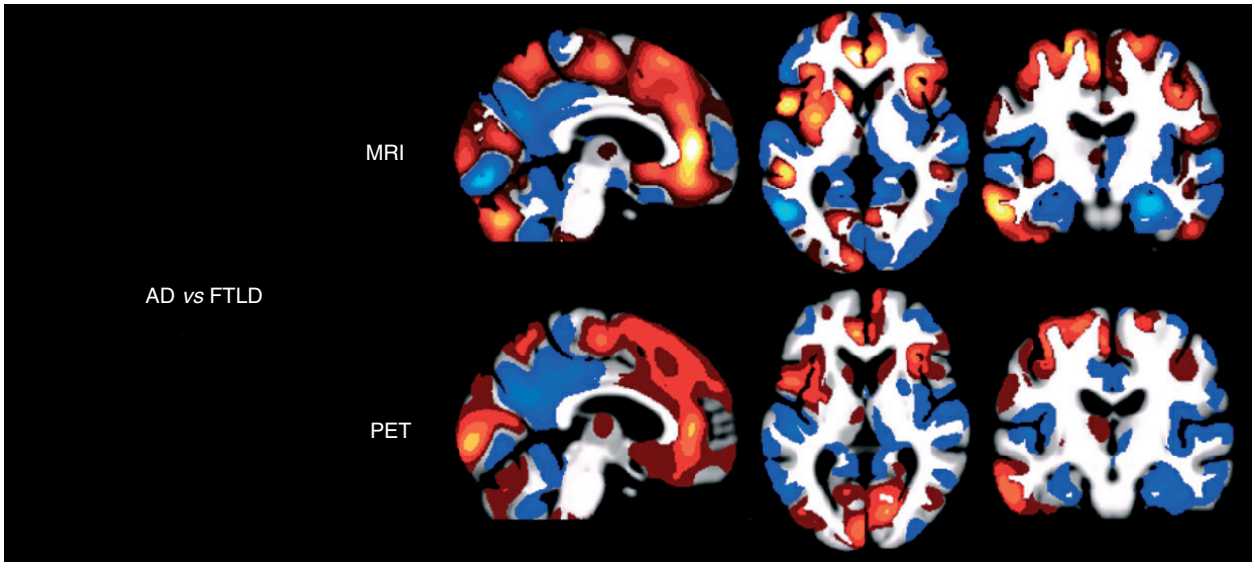

Figure 3. The combined use of MRI and PET with the FDG-PET radioligand provided the highest accuracy for detection and discrimination of patients with AD relative to those with FTLD. The regions in red are the most discriminative for FTLD patients, while the blue regions are the most discriminative for AD patients in terms of MRI and PET signal.

presence of early cognitive symptoms (including visual hallucinations) is recognized as an important clinical discriminant between DLB and PDD, in which the cognitive symptoms typically develop later in the course of the disease and usually after the full manifestation of the motor disorder[39]. A part for the temporal evolution of the cognitive problems in PDD and DLB, the clinical features of these disorders are highly overlapping. It has been estimated that up to 70% of patients with Parkinson's disease develop at a certain stage of their disease trajectory some cognitive dysfunctions. Typical cognitive problems include visual hallucinations, deficits in visuo-spatial skills, impairments in executive functions such as attention or working-memory, and speech difficulty (e.g., reduced verbal fluency). At the pathological level, PDD and DLB can also be characterized by amyloid accumulation and more recently the potential presence of tau pathology in PDD and DLB has also been recognized[19]. This implies that the complexity of the molecular pathophysiology in PDD and DLB can span over other common neurodegenerative disorders including AD and FTLD syndromes. The lack of clear clinical and pathological 'borders' across PDD, DLB, AD, and FTLD syndromes represents thus a diagnostic challenge which will become even more pronounced when new therapeutic options targeting different molecular pathways will be available for these conditions[19].

❒ Molecular imaging in PDD and DLB

Consistently with the clinical spectrum of these disorders, past SPECT and FDG PET studies have reported decreased perfusion and glucose metabolism in posterior cortical regions in PDD and DLB[56]. These regions include the occipital and temporo-parietal regions as well as the basal ganglia, cerebellum, and frontal cortices[56]. Interestingly, there was a relative sparing of the medial temporal lobe areas in terms of FDG PET metabolism which is in keeping with the less pronounced episodic memory problems displayed by these patients especially when compared to those with AD[56]. Decreased FDG PET metabolism in posterior visual cortices also related to frequency and severity of visual hallucinations which supports the clinical utility of FDG PET in tracking the symptomatology of PPD and DLB[18]. Likewise, decreased SPECT DAT binding in the basal ganglia has been found to correlate with cognitive symptoms in patients with PDD and DLB, while reduced dopaminergic transporter binding in the putamen was found to relate to the severity of motor problems[62].
Around 40% of patients with DLB have also been found to display positive amyloid PET scan[23] (Figure 4). The specificity of the positivity of the amyloid scan for cognitive problems in DLB is further corroborated by the fact that PD without dementia show a less significant binding of the ^{11}CPiB PET

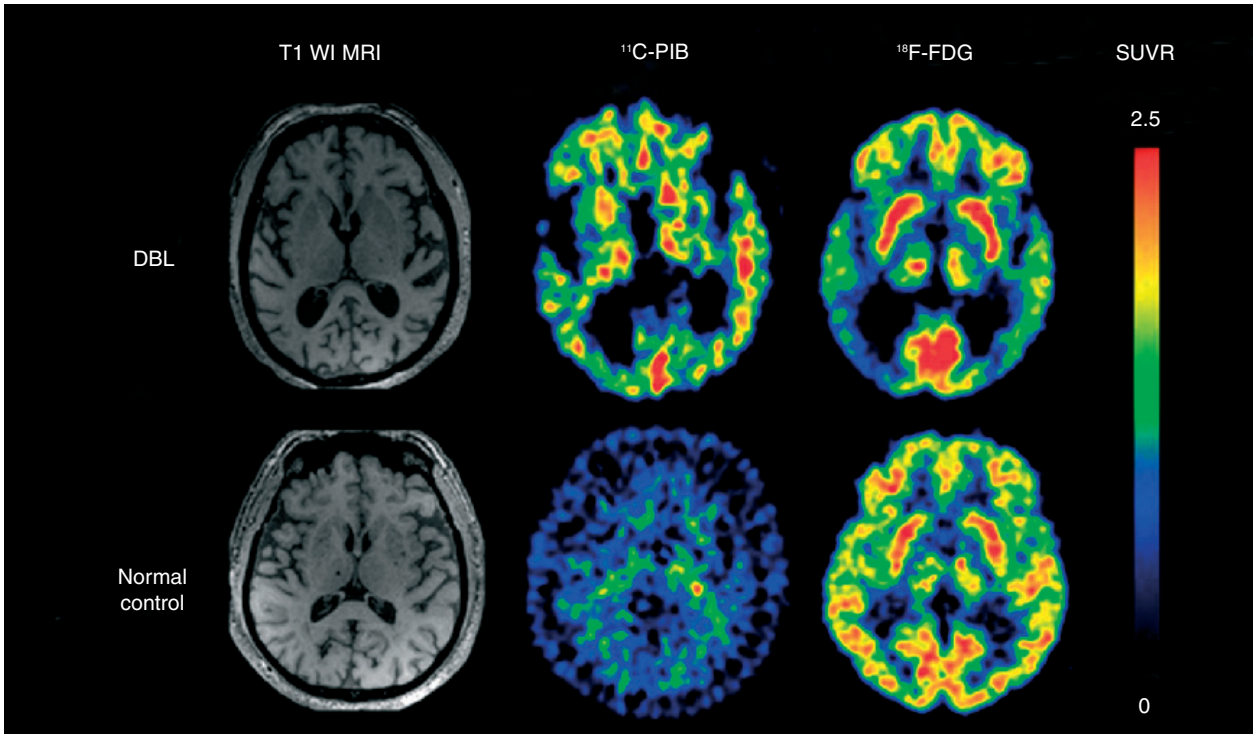

Figure 4. Structural MRI, amyloid (^{11}C-PIB) and FDG PET scan in a patients with dementia with Lewy bodies relative to a normal control. While the MRI scan do not show prominent changes the amyloid and glucose metabolism PET scans are able to show amyloid accumulation in the DLB patient and reduced glucose metabolism in occipito-parietal regions which is consistent with the clinical syndrome (*Modified from Liu et al., 2018*[40]).

tracer[57]. While new PET tracers for the main pathological hallmark of PDD and DLB (alpha-synuclein) remain under-develop, some recent studies have shown that PET tau tracers such as AV-1451 might have some clinical utility in detecting the typical neurodegeneration in the substantia nigra that characterize these disorders[68]. Although this effect seems to be dependent on the 'off-target' binding properties of the AV-1451 tracer (i.e., 'off-target' binding to neuromelanin)[26]; it might be possible that the AV-1451 tracer may still offer some useful information and insight to help developing new in vivo biomarkers for PDD and DLB[26].

☐ MOLECULAR IMAGING IN THE DIFFERENTIAL DIAGNOSIS OF NEURODEGENERATIVE FORMS OF DEMENTIA

As highlighted several times throughout this review, the presence of overlapping clinical and pathological features in the neurodegenerative disorders that lead to dementia syndromes poses a challenge to the differential diagnosis amongst these conditions and inevitably confound the patient selection in clinical trials targeting distinct molecular pathways.

A promising way of addressing and tackling such complexity is to use advanced and novel molecular imaging biomarkers that can reliably quantify *in vivo* the specific pathological changes associated with different neurodegenerative disorders.

In the near future, I envisage the use of biomarkers like PET with amyloid and/or tau tracer to provide a good discrimination between AD-related and FTLD-related syndromes. Atypical forms of AD including patients with cortico-basal syndrome will be better characterized by the combined use of tau and amyloid tracers. The use of well-established markers of nigro-striatal degeneration (DAT SPECT) or glucose metabolism (FDG PET) remains invaluable to characterize the presence of dopaminergic deficits and areas of hypometabolism and to complement the more novel PET biomarkers. Due to space limitations, this review does not describe the attempts and effort to validate other important neuroimaging

measures in dementia and neurodegenerative disorders, including structural and functional MRI. These techniques are less expensive and less invasive alternatives of PET and SPECT biomarkers and are more indicated to assess the level of atrophy and functionally-relevant effects of the neurodegenerative processes. In the future it is possible that new and multi-modal markers will be develop by integrating large arrays of measures including clinical, MRI-based, and molecular imaging-derived biomarkers. This highly complex set of data holds the promise of providing a more powerful characterization of the patient's specific clinical, pathological, and brain features that would enable the development of personalized therapies alongside individualized health care for improved prognostication, therapies, and clinical management. Sophisticated algorithms based on machine learning approaches and artificial intelligence methods have been recently implemented in the revolutionary field of Precision Medicine applied to neurodegenerative conditions, although their utility in the everyday clinical practice remains to be ascertained and fully tested[53].

□ CONCLUSION

Molecular imaging studies in neurodegenerative conditions leading to dementia are highly informative regarding the clinical, pathological, and brain features underpinning an overlapping group of clinical disorders. Advanced imaging techniques hold the promise to improve the differential diagnosis across these conditions and can be helpful to track the disease progression or monitor the potential effects of disease-modifying therapies. An improved stratification of patients based on objective and reliable measures that are able to quantify the molecular complexity of each neurodegenerative disorder is urgently needed to de-risk and empower upcoming clinical trials.

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Disclosure. *The Author declare no conflicts of interest.*

Progress in
Neuroscience

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PRINT ISSN 2240-5127
ON-LINE ISSN 2240-5135

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Authorized by the *Tribunale in Trento*, 11th May 2011 - Registration: *Registro della Stampa* n. 18 and *Registro degli Operatori di Comunicazione* (ROC) n. 3810 - *Quarterly*.

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